EXHIBIT A - PART 4 OF 7

Electronic Acknowledgement Receipt

EFS ID:	11667298
Application Number:	12229074
International Application Number:	
Confirmation Number:	7450
Title of Invention:	Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione
First Named Inventor/Applicant Name:	Jerome B. Zeldis
Customer Number:	84802
Filer:	Yeahsil Moon/Rochelle Flowers
Filer Authorized By:	Yeahsil Moon
Attorney Docket Number:	9516-773-999
Receipt Date:	20-DEC-2011
Filing Date:	19-AUG-2008
Time Stamp:	16:22:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$560
RAM confirmation Number	3870
Deposit Account	503013
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	Amendment_and_Response.pdf	461495 42f8ba81abff21800c25ef656a8ad8c8daa76bce	no	11
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
2	Rule 130, 131 or 132 Affidavits	Exhibit_1_Schey_Expert_Opinion_2011.pdf	812037 73f4cd37da6b64fc0e2b80a4f0877df981645c51	no	11
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
3	Rule 130, 131 or 132 Affidavits	Exhibit_2_Lacy_Blood_2011.pdf	529534 ae5776a3993c7fee5b05b01ffcf9f0b26868b5ed	no	7
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
4	Extension of Time	EOT.pdf	29422 11c4fc158d3cb9af79e9952e78bc1daec920f909	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30261 13d948bee90c9adb96b392561b9b41cbd3282cef	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1862749		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/229,074	08/19/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/20/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 11	Minus	** 35	= 0	X $ =		OR	X $60=	0
Independent (37 CFR 1.16(h))	* 1	Minus	***2	= 0	X $ =		OR	X $250=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/CHERYL CLARK/

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999	7450

84802 7590 03/06/2012

JONES DAY for Celgene Corporation
222 E. 41ST. STREET
NEW YORK, NY 10017

EXAMINER	
SIMMONS, CHRIS E	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
03/06/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Applicant-Initiated Interview Summary	**Application No.** 12/229,074	**Applicant(s)** ZELDIS, JEROME B.	
	Examiner CHRIS SIMMONS	**Art Unit** 1612	

All participants (applicant, applicant's representative, PTO personnel):

(1) *CHRIS SIMMONS*.

(2) *FREDERICK KRASS*.

(3) *YEAH SIL-MOON*.

(4) *DONNA ROBERTSON-CHOW*.

Date of Interview: *01 March 2012*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *al* .

Identification of prior art discussed: *of record*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed potential allowabilty of claims if independent claims are amended to incorporate the limitations of claim 1 of U.S. Pat 7,968,569. Particularly the cyclical admininstration of the current amounts of the compound.for 21 consecutive days.followed by 7 consecutive days of rest from administration of the compound in a 28 day cycle in combination with 40 mg of dexamethasone. .

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/CHRIS SIMMONS/ Examiner, Art Unit 1612	/Frederick Krass/ Supervisory Patent Examiner, Art Unit 1612

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

ELECTRONIC FILING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis	Confirmation No.: 7450
Serial No.: 12/229,074	Group Art Unit: 1612
Filed: August 19, 2008	Examiner: Simmons, Chris E.
For: METHOD FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3-DIONE (as amended)	Attorney Docket No.: 9516-773-999 (CAM: 501872-999773)

RESPONSE AND STATEMENT OF INTERVIEW SUMMARY

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to Response filed on December 20, 2011 responding to Office Action dated August 9, 2011, Examiner interview held on March 1, 2012, and in response to Interview Summary dated March 6, 2012, Applicant submits the following amendment and remarks for the consideration by the Examiner and entry into the record of the above-captioned application.

Amendments to the Claims are reflected in the listing of the claims that begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

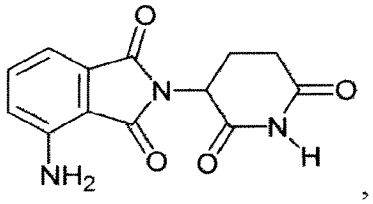
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of the Claims:

Claims 1-60. (canceled)

61. (new) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma: (a) from about 1 mg to about 4 mg per day of a compound 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione having the formula:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof for 21 consecutive days followed by seven consecutive days of rest from administration of said compound in a 28 day cycle, and (b) 40 mg of dexamethasone.

62. (new) The method of claim 61, wherein the multiple myeloma is relapsed and refractory multiple myeloma.

63. (new) The method of claim 61, wherein the multiple myeloma is newly diagnosed multiple myeloma.

64. (new) The method of claim 61, wherein the multiple myeloma is refractory multiple myeloma.

65. (new) The method of claim 61, wherein the multiple myeloma is relapsed multiple myeloma.

66. (new) The method of claim 61, wherein the patient has received previous therapy.

67. (new) The method of claim 61, wherein the patient has demonstrated disease progression on previous therapy.

68. (new) The method of claim 61, wherein the patient has received previous therapy and has demonstrated disease progression on previous therapy.

69. (new) The method of claim 61, wherein the patient has previously received 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and a proteasome inhibitor.

70. (new) The method of claim 66, 67 or 68, wherein the previous therapy is

treatment with thalidomide, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, a proteasome inhibitor, stem cell transplantation, or a combination thereof.

71. (new) The method of claim 61, wherein the compound is administered in an amount of about 4 mg per day.

72. (new) The method of claim 61, wherein the compound is administered in an amount of about 3 mg per day.

73. (new) The method of claim 61, wherein the compound is administered in an amount of about 2 mg per day.

74. (new) The method of claim 61, wherein the compound is administered in an amount of about 1 mg per day.

75. (new) The method of claim 61, where the dexamethasone is orally administered in an amount of 40 mg once daily on days 1, 8, 15 and 22 of each 28 day cycle.

76. (new) The method of claim 61, wherein the dexamethasone is orally administered in an amount of about 40 mg once a week of each 28 day cycle.

77. (new) The method of claim 61, wherein the compound is administered in a capsule.

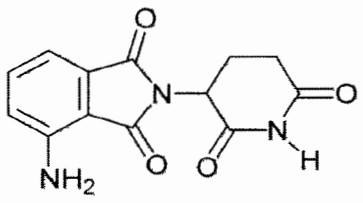
78. (new) The method of claim 61, wherein the compound is administered in a tablet.

79. (new) The method of claim 61, wherein the compound is administered orally in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg.

80. (new) The method of claim 79, wherein the capsule comprises the compound, mannitol and pre-gelatinized starch.

81. (new) A method of treating relapsed and refractory multiple myeloma, which comprises:

(1) administering to a patient having multiple myeloma (a) about 1 mg to about 4 mg per day of a compound 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione having the formula:

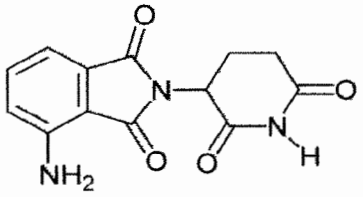


for 21 consecutive days followed by seven consecutive days of rest from administration of said compound in a 28 day cycle, and (b) 40 mg of dexamethasone; and

(2) wherein the patient has received previous therapy with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and a proteasome inhibitor.

82. (new) A method of treating relapsed and refractory multiple myeloma, which comprises:

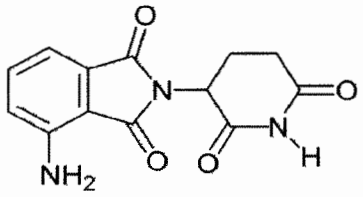
(1) administering to a patient having multiple myeloma (a) about 1 mg to about 4 mg per day of a compound 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione having the formula:



for 21 consecutive days followed by seven consecutive days of rest from administration of said compound in a 28 day cycle, and (b) 40 mg of dexamethasone; and

(2) wherein the patient has received previous therapy with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and a proteasome inhibitor, and the patient has demonstrated disease progression on previous therapy.

83. (new) A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma: (a) from about 1 mg to about 4 mg per day of a compound 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione having the formula:



for 21 consecutive days followed by seven consecutive days of rest from administration of said compound in a 28 day cycle, and (b) 40 mg of dexamethasone on at least one of days 1-21 of said cycle.

84. (new) The method of claim 81, 82 or 83, wherein the compound is administered in an amount of about 4 mg per day.

85. The method of claim 81, 82 or 83, wherein the compound is administered in an amount of about 3 mg per day.

86. The method of claim 81, 82 or 83, wherein the compound is administered in an amount of about 2 mg per day.

87. The method of claim 81, 82 or 83, wherein the compound is administered in an amount of about 1 mg per day.

88. (new) The method of claim 81, 82 or 83, wherein the dexamethasone is administered once daily on days 1, 8, 15 and 22 in a 28 day cycle.

89. (new) The method of claim 81, 82 or 83, wherein the compound is administered in a capsule of 1 mg, 2 mg, 3 mg, or 4 mg.

90. (new) The method of claim 89, wherein the capsule comprises the compound, mannitol and pre-gelatinized starch.

91. (new) The method of claim 61, where the compound is a pharmaceutically acceptable salt, solvate or stereoisomer.

92. (new) The method of claim 83, where the multiple myeloma is relapsed and refractory multiple myeloma.

REMARKS

I. Applicant's Statement of the Substance of Interview and Response to the Examiner's Interview Summary of Record

A telephonic interview with Supervisory Patent Examiner Frederick Krass, Patent Examiner Chris E. Simmons, Dr. Donna Robertson-Chow (Celgene Corporation, the assignee of this application), and Yeah-Sil Moon (attorney for Applicant), was held on March 1, 2012. Applicant appreciates the Examiner interview.

During the interview, the Examiners and attorney for Applicant discussed allowability of the claims and the amendment to the claims.

The Examiners stated that the claims would be allowed if independent claims are amended to incorporate the cyclic administration of the current amounts of the compound for 21 consecutive days followed by seven consecutive days of rest from administration of the compound in a 28 day cycle in combination with 40 mg of dexamethasone. *See Interview Summary.*

Without acquiescing to the merits of the rejections and solely to promote allowance of this case, Applicant amended the claims as suggested by the Examiners.

Applicant respectfully points out that the Office Action dated August 9, 2011 withdrew all the double patenting rejections and only maintained rejections under 35 U.S.C. § 103(a). (Pages 2-7 of the Office Action). In the December 20, 2011 Response, Applicant submitted the arguments as to the differences of the claimed invention from the cited references, and unexpected results that are sufficient to rebut any presumption of obviousness cited in the Office Action. In view of the Response and the present amendment, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be withdrawn.

II. Conclusion

In view of the foregoing, all the rejections are moot and the case should proceed to allowance. Entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: March 15, 2012

Yeah-Sil Moon (Reg. No. 52,042)
For Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
222 East 41st Street
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Electronic Acknowledgement Receipt

EFS ID:	12312253
Application Number:	12229074
International Application Number:	
Confirmation Number:	7450
Title of Invention:	Methods for treating multiple myeloma using 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3dione
First Named Inventor/Applicant Name:	Jerome B. Zeldis
Customer Number:	84802
Filer:	Yeahsil Moon/Rochelle Flowers
Filer Authorized By:	Yeahsil Moon
Attorney Docket Number:	9516-773-999
Receipt Date:	15-MAR-2012
Filing Date:	19-AUG-2008
Time Stamp:	13:44:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	Response_and_Statement_of_Interview_Summary.pdf	229307 bc0124d78367f07f0cff3963d2ee2f041e9ebcf3	no	7

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Information:

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/229,074	Filing Date 08/19/2008	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/15/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 47	Minus	** 35	= 12	X $ =		OR	X $60=	720
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**720**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/MARISSA BLYTHER/

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 03/27/2012

MBLYTHER	SALE	#00000001	Mailroom Dt: 03/15/2012	503013	12229074	
		01	FC : 1203	450.00 DA		
		02	FC : 1202	720.00 DA		

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

84802 7590 04/09/2012
JONES DAY for Celgene Corporation
222 E. 41ST. STREET
NEW YORK, NY 10017

EXAMINER
SIMMONS, CHRIS E

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 04/09/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999	7450

TITLE OF INVENTION: METHODS FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3DIONE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	07/09/2012

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

84802 7590 04/09/2012
JONES DAY for Celgene Corporation
222 E. 41ST. STREET
NEW YORK, NY 10017

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999	7450

TITLE OF INVENTION: METHODS FOR TREATING MULTIPLE MYELOMA USING 4-(AMINO)-2-(2,6-DIOXO(3-PIPERIDYL))-ISOINDOLINE-1,3DIONE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	07/09/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
SIMMONS, CHRIS E	1612	514-058000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
❑ Issue Fee
❑ Publication Fee (No small entity discount permitted)
❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
❑ A check is enclosed.
❑ Payment by credit card. Form PTO-2038 is attached.
❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/229,074	08/19/2008	Jerome B. Zeldis	9516-773-999	7450

84802 7590 04/09/2012

JONES DAY for Celgene Corporation
222 E. 41ST. STREET
NEW YORK, NY 10017

EXAMINER	
SIMMONS, CHRIS E	

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 04/09/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 139 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 139 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	12/229,074	ZELDIS, JEROME B.	
	Examiner	Art Unit	
	CHRIS SIMMONS	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed on 03/15/2012*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *61-68, 70-80 and 83-92*.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 12/23/2010
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/CHRIS SIMMONS/ Examiner, Art Unit 1612	/Frederick Krass/ Supervisory Patent Examiner, Art Unit 1612

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Yeah-Sil Moon on 03/21/12.

The following changes have been made:

1) Claim 61, second line and claim 83, second line, in each instance "4" has been changed to --- 5 ----

2) Claim 61, third line, and claim 83, third line, in each instance"4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione --- has been deleted.

3) Claim 70, "67 or 68," has been deleted.

4) Claims 69, 81 and 82 have been canceled without prejudice thereto.

5) Claims 84-89, first line of each claim, in each instance "81, 82 or" has been deleted.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRIS SIMMONS whose telephone number is (571)272-9065. The examiner can normally be reached on Monday - Friday from 7:30 - 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CHRIS SIMMONS/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12229074	ZELDIS, JEROME B.
Examiner	**Art Unit**
CHRIS SIMMONS	1612

ORIGINAL		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	58	A 0 1 N 43 / 40 (2006.0)	

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	323	329	330		

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		17		33		49	5	65	-	81				
	2		18		34		50	6	66	-	82				
	3		19		35		51	7	67	20	83				
	4		20		36		52	8	68	21	84				
	5		21		37		53	-	69	22	85				
	6		22		38		54	9	70	23	86				
	7		23		39		55	10	71	24	87				
	8		24		40		56	11	72	25	88				
	9		25		41		57	12	73	26	89				
	10		26		42		58	13	74	27	90				
	11		27		43		59	14	75	28	91				
	12		28		44		60	15	76	29	92				
	13		29		45	1	61	16	77						
	14		30		46	2	62	17	78						
	15		31		47	3	63	18	79						
	16		32		48	4	64	19	80						

/CHRIS SIMMONS/ Examiner.Art Unit 1612 (Assistant Examiner)	03/21/2012 (Date)	**Total Claims Allowed:** 29
/FREDERICK KRASS/ Supervisory Patent Examiner.Art Unit 1612 (Primary Examiner)	03/26/2012 (Date)	O.G. Print Claim(s) 1 O.G. Print Figure NONE

LIST OF REFERENCES CITED BY APPLICANT

(Use several sheets if necessary)

Application Number	12/229,074
Filing Date	August 19, 2008
First Named Inventor	Jerome B. Zeldis
Art Unit	1612
Examiner Name	Simmons, Chris E.
Attorney Docket No.	9516-773-999

U.S. PATENT DOCUMENTS

*Examiner Initials	Cite No.	Document Number – Kind Code	Publication Date mm/dd/yyyy	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A83	7,435,745	10/14/2008	Celgene Corporation	
	A84	7,393,862	07/01/2008	Celgene Corporation	

FOREIGN PATENT DOCUMENTS

*Examiner Initials	Cite No.	Foreign Patent Document Country Code, Number, Kind Code (if known)	Publication Date mm/dd/yyyy	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	B01	WO 02/015926	02/28/2002	Kirin Beer Kabushiki Kaisha		
	B09	WO 92/14455	09/03/1992	The Rockefeller University		
	B10	WO 94/20085	09/15/1994	Children's Hospital Medical Center Corporation		

NON PATENT LITERATURE DOCUMENTS

*Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
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	C208	List, A., "New Approaches to the Treatment of Myelodysplasia," *The Oncologist*, 2002, 7(suppl. 1):39-49	
	C209	Kurzrock, R., "Myelodysplastic syndrome overview," *Seminars in Hematology* (Abstract only), 2002, 39(3)(suppl. 2):18-25 *Abstract only*	
	C210	Goerner, *et al.*, "Morbidity and mortality of chronic GVHD after hematopoietic stem cell transplantation from HLA-identical siblings for patients with aplastic or refractory anemias," *Biology of Blood and Marrow Transplantation* (Abstract only), 2002, 8(1):47-56	
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	C215	Kon-nichi no Chiryou Shishin, 1997 [Pocket Edition], Igaku Shoin, 1997, 513-514 (in Japanese)	√*
	C216	Okamoto, T., Kotsuzuiikeisei Shoukougun to Men-eki Ijo, Bessatsu Nihon Rinsho, Syndrome Series for each area, No. 22, Blood Syndromes III, Nihon Rinshou, 213-216 (in Japanese) Oct 1998	√*
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NYI-4336212v1

EXAMINER SIGNATURE	/Chris Simmons/	**DATE CONSIDERED**	07/30/2011

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /C.S./

LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)		
	Application Number	12/229,074
	Filing Date	August 19, 2008
	First Named Inventor	Jerome B. Zeldis
	Art Unit	1612
	Examiner Name	Simmons, Chris E.
	Attorney Docket No.	9516-773-999

NON PATENT LITERATURE DOCUMENTS

*Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	C218	Copy of Notice of Allowance from U.S. Patent Application No. 11/096,155 dated January 12, 2010	
	C219	Rajkumar et al., "Combination therapy with thalidomide plus dexamethasone for newly diagnosed multiple myeloma," *American Society of Hematology*, 43rd Annual Meeting, Dec. 7-11, 2001, Abstract #3525	
	C220	Scheffler et al., "Safety and pharmacokinetics of CDC-501, a novel immunomodulatory-oncologic agent, after single then multiple, oral 100 mg twice daily doses," *American Society for Clinical Pharmacology and Therapeutics*, March 24-27, 2002, Abstract #WPIII-63	
	C221	Marriott et al., "Thalidomide analogue CDC-501 is safe and well tolerated by patients with end stage cancer and shows evidence of clinical responses and extensive immune activation," *Br. J. Cancer*, 2002, 86(Supp. 1):Abst 6.4	
	C222	Kast, R.E., "Evidence of a mechanism by which etanercept increased TNF-alpha in multiple myeloma: New insights into the biology of TNF-alpha giving new treatment opportunities – the role of burproion," *Leukemia Research*, 2005, 29:1459-1463	
	C223	Tsimberidou, A. et al., "Pilot study of recombinant human soluble tumor necrosis factor (TNF) receptor (p75) fusion protein (TNFR:Fc;Enbrel) in patients with refractory multiple myeloma: increase in plasma TNFα levels during treatment," *Leukemia Research*, 2003, 27:375-380	
	C224	Dimopoulos, et al., "Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma," *Leukemia*, 2009, 1-6	
	C225	Hideshima, T., et al., "A review of lenalidomide in combination with dexathasone for the treatment of multiple myeloma," *Therapeutics and Clinical Risk Management*, 2008, 4(1):129-136	
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	C229	Richardson, P. *et al.*, "Thalidomide in multiple myeloma," *Biomed Pharmacother*, 2002, 56:115-28	
	C230	Swartz, G. *et al.*, "Pre-clinical evaluation of ENMD-0995: A thalidomide analog with activity against multiple myeloma and solid tumors," *Cell and Tumor Biology*, 2002, 43:181-182, Abstract# 910	
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	C236	Copy of Notification letter dated 8/30/10 from Natco Pharma Limited to Celgene Corporation re: Notification purusant to § 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act	
	C237	Copy of Complaint for Patent Infringement filed on 10/8/10 by Celgene Corporation in the U.S. District Court, District of New Jersey against Natco Pharma Limited	
	C238	Copy of Answer to Complaint filed on 11/18/10 by Natco Pharma Limited in the U.S. District Court, District of New Jersey	

Examiner added publication dates for references C207, C216 and C232 that were provided by applicant's representative

EXAMINER SIGNATURE	/Chris Simmons/	**DATE CONSIDERED**	07/30/2011

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	Filing Date	August 19, 2008
	First Named Inventor	Jerome B. Zeldis
	Art Unit	1612
	Examiner Name	Simmons, Chris E.
	Attorney Docket No.	9516-773-999

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*Examiner Initials	Cite No.	Include name of the author (in CAPITAL LETTERS), (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	C239	Grosshans, E. and Illy, G., "Thalidomide Therapy for Inflammatory Dermatoses," *International Journal of Dermatology*, 1984, 23(9):598-602	
	C240	Krenn, M. *et al.*, "Improvements in Solubility and Stability of Thalidomide upon Complexation with Hydropropyl-β-Cyclodextrin," *Journal of Pharmaceutical Sciences*, 1992, 81(7):685-689	
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	C243	Smith, R. *et al.*, "Studies on the Relationship Between the Chemical Structure and Embryotoxic Activity of Thalidomide and Related Compounds," in *A Symposium on Embryopathic Activity of Drugs*, J. & A. Churchill Ltd., 1965, Session 6, pp. 194-209	
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	C246	Raje, N. and Anderson, K., "Thalidomide and immunomodulatory drugs as cancer therapy," *Current Opinions in Oncology*, 2002, 14:635-640	
	C247	Kumar, S. *et al.*, "Thalidomide as an anti-cancer agent," *J. Cell. Mod. Med.*, 2002, 6(2):160-174	
	C248	Singhal, S. and Mehta, J., "Thalidomide in Cancer," *BioDrugs*, 2001, 15(3):163-172	
	C249	Copy of Notice of Opposition to EP 1 505 973 filed by Synthon B.V. on November 30, 2010	
	C250	Copy of Notice of Opposition to EP 1 505 973 filed by Strawman Limited on December 1, 2010	
	C251	Samson, D. *et al.*, "Infusion of Vincristine and Doxorubicin with Oral Dexamethasone as First-Line Therapy for Multiple Myeloma," *The Lancet*, 1989, 334(8668):882-885	
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*cited in C213

NYI-4336212v1

EXAMINER SIGNATURE	/Chris Simmons/	DATE CONSIDERED	07/30/2011

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STN search for 12/229,074

N FILE 'REGISTRY' AT 19:47:58 ON 21 MAR 2012

=> s L20 FUL

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 203.25 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:Y

FULL SEARCH INITIATED 19:50:24 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 3984 TO ITERATE

100.0% PROCESSED 3984 ITERATIONS 3 ANSWERS

SEARCH TIME: 00.00.01

L23 3 SEA SSS FUL L20

=> D 1-

YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):Y

L23 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2012 ACS on STN

RN 202271-90-7 REGISTRY

ED Entered STN: 05 Mar 1998

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-2,6-dioxo-3-piperidinyl]- (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(2,6-dioxo-3-piperidinyl)-, (R)-

FS STEREOSEARCH

MF C13 H11 N3 O4

SR CA

LC STN Files: CA, CAPLUS, CASREACT, IMSRESEARCH, TOXCENTER, USPAT2,
USPATFULL

Absolute stereochemistry. Rotation (+).

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

10 REFERENCES IN FILE CA (1907 TO DATE)

10 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L23 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2012 ACS on STN

RN 202271-89-4 REGISTRY

ED Entered STN: 05 Mar 1998

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-2,6-dioxo-3-piperidinyl]- (CA
INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(2,6-dioxo-3-piperidinyl)-, (S)-

OTHER NAMES:

CN (S)-4-Amino-2-(2,6-dioxo-3-piperidinyl)isoindole-1,3-dione

CN (S)-CC-4047

FS STEREOSEARCH

MF C13 H11 N3 O4

SR CA

LC STN Files: CA, CAPLUS, CASREACT, CHEMCATS, IMSRESEARCH, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (-).

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

14 REFERENCES IN FILE CA (1907 TO DATE)

14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L23 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2012 ACS on STN

RN 19171-19-8 REGISTRY

ED Entered STN: 16 Nov 1984

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(2,6-dioxo-3-piperidinyl)- (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Phthalimide, 3-amino-N-(2,6-dioxo-3-piperidyl)- (8CI)

OTHER NAMES:

CN 4-Amino-2-(2,6-dioxo-3-piperidinyl)isoindole-1,3-dione

CN 4-Amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione

CN Actimid

CN CC 4047

CN IMiD 3

CN Pomalidomide

DR 443912-23-0, 443919-33-3

MF C13 H11 N3 O4

LC STN Files: ADISINSIGHT, AGRICOLA, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, EMBASE, IMSRESEARCH, IPA, MEDLINE, MRCK*, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

197 REFERENCES IN FILE CA (1907 TO DATE)

8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

203 REFERENCES IN FILE CAPLUS (1907 TO DATE)

FILE 'REGISTRY' ENTERED AT 19:35:55 ON 21 MAR 2012

L17 STRUCTURE UPLOADED

L18 2 S L17

L19 0 S FAM L18

L20 STRUCTURE UPLOADED

L21 0 S L20

L22 0 S L20 FAM

L23 3 S L20 FUL

FILE 'USPATFULL' ENTERED AT 19:50:57 ON 21 MAR 2012

L24 124 S L23

=> S L24 AND MYELOMA/CLM

4737 MYELOMA/CLM

164 MYELOMAS/CLM

4874 MYELOMA/CLM

((MYELOMA OR MYELOMAS)/CLM)

L25 24 L24 AND MYELOMA/CLM

=> D L25 PN CLM 1-

YOU HAVE REQUESTED DATA FROM 24 ANSWERS - CONTINUE? Y/(N):Y

THE ESTIMATED COST FOR THIS REQUEST IS 60.00 U.S. DOLLARS

DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L25 ANSWER 1 OF 24 USPATFULL on STN

PI US 20120035145 A1 20120209

CLM What is claimed is:

1-18. (canceled)

19. A method of treating multiple myeloma in a human patient which comprises: (1) induction therapy which comprises sequentially or simultaneously administering to a patient having multiple myeloma: (a) melphalan: (b) prednisone; and (c) about 5 to about 25 mg per day of a compound of the formula: ##STR9## or a pharmaceutically acceptable salt thereof: (2) followed by maintenance therapy which comprises administering to the patient 5 to about 25 mg per day of the compound or the pharmaceutically acceptable salt thereof until disease progression or unacceptable toxicity.

20. The method of claim 19, wherein the multiple myeloma is newly diagnosed multiple myeloma.

21. The method of claim 19, wherein the compound is administered orally.

22. The method of claim 19, wherein the induction therapy comprises nine 28-day cyces.

23. The method of claim 19, wherein the compound is administered in an amount of about 10 mg per day.

24. The method of claim 19, the compound is administered in the form of a capsule.

25. The method of claim 24, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

26. The method of claim 19, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

27. A method of treating multiple myeloma which comprises: (1) induction therapy which comprises administering to a patient having multiple myeloma: (a) melphalan on days 1-4 every 28 days; (b) prednisone on days 1-4 every 28 days; and (c) about 5 to about 25 mg per day of a compound of the formula: ##STR10## or a pharmaceutically acceptable salt hereof, on days 1-21 every 28 days; (2) followed by maintenance therapy which comprises administering to the patient 5 to about 25 mg per day of the compound or the pharmaceutically acceptable salt thereof on days 1-21 every 28 days until disease progression or unacceptable toxicity.

28. The method of claim 27, wherein the multiple myeloma is newly diagnosed multiple myeloma.

29. The method of claim 27, wherein the compound is administered orally.

30. The method of claim 29, the compound is administered in the form of a capsule.

31. The method of claim 30, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

32. The method of claim 27, wherein the induction therapy comprises nine 28-day cycles.

33. The method of claim 27, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

34. The method of claim 27, wherein the compound is administered in a capsule of 10 mg.

35. A method of treating multiple myeloma which comprises: (1) administering to a patient having multiple myeloma: (a) melphalan on days 1-4 every 28 days; (b) prednisone on days 1-4 every 28 days; and (c) about 10 mg per day of a compound of the formula: ##STR11## on days 1-21 every 28 days; (2) followed by maintenance therapy which comprises

administering to the patient 10 mg per day of the compound on days 1-21 every 28 days after step (1).

36. The method of claim 35, wherein the multiple myeloma is newly diagnosed multiple myeloma.

37. The method of claim 35, wherein the compound is administered orally.

38. The method of claim 35, the compound is administered in the form of a capsule.

39. The method of claim 38, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

40. The method of claim 35, wherein the induction therapy comprises nine 28-day cycles.

41. The method of claim 35, wherein the compound is administered in a capsule of 5 mg or 10 mg.

42. The method of claim 35, wherein the compound is administered in a capsule of 10 mg.

L25 ANSWER 2 OF 24 USPATFULL on STN

PI US 20110280849 A1 20111117

CLM What is claimed is:

1. A method of treating an individual having cancer, comprising administering to said individual isolated natural killer cells comprising isolated CD56.sup.+, CD16.sup.- placental intermediate natural killer cells, wherein said cancer is acute promyelocytic leukemia, acute myeloblastic leukemia, acute megakaryoblastic leukemia, precursor B acute lymphoblastic leukemia, precursor T acute lymphoblastic leukemia, Burkitt's leukemia (Burkitt's lymphoma), acute biphenotypic leukemia, chronic monocytic leukemia, chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma, B-cell prolymphocytic leukemia; hairy cell lymphoma; T-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, plasmacytoma, a monoclonal immunoglobulin deposition disease, or a heavy chain disease, extranodal marginal zone B cell lymphoma (MALT lymphoma), nodal marginal zone B cell lymphoma (NMZL), follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, T cell large granular lymphocytic leukemia, aggressive NK cell leukemia, extranodal NK/T cell lymphoma, nasal type, enteropathy-type T cell lymphoma, hepatosplenic T cell lymphoma, blastic NK cell lymphoma, mycosis fungoides (Sezary

syndrome), a primary cutaneous CD30-positive T cell lymphoproliferative disorder, primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, angioimmunoblastic T cell lymphoma, peripheral T cell lymphoma, unspecified, anaplastic large cell lymphoma, a Hodgkin lymphoma, a nodular lymphocyte-predominant Hodgkin lymphoma, a retinoblastoma, or a colorectal carcinoma.

2. The method of claim 1, wherein said natural killer cells are additionally CD3.sup.-.

3. The method of claim 1 additionally comprising administering to said individual an effective amount of lenalidomide, pomalidomide, or thalidomide.

4. The method of claim 1, wherein said isolated natural killer cells have been contacted with pomalidomide, lenalidomide, or thalidomide prior to said administering.

5. The method of claim 1 wherein said natural killer cells comprise natural killer cells not obtained from placental perfusate.

6. The method of claim 1 wherein said natural killer cells are combined natural killer cells that comprise natural killer cells isolated from placental perfusate and natural killer cells isolated from umbilical

cord blood.

7. The method of claim 6 wherein said umbilical cord blood is isolated from the placenta from which said placental perfusate is obtained.

8. The method of claim 3 wherein said natural killer cells are contacted with said pomalidomide, lenalidomide, or thalidomide in an amount and for a time sufficient for said natural killer cells to express detectably more granzyme B, or mRNA encoding granzyme B, than an equivalent number of natural killer cells not contacted with said pomalidomide, lenalidomide, or thalidomide.

9. The method of claim 6, wherein said combined natural killer cells comprise: a detectably higher number of CD3.sup.-CD56.sup.+CD16.sup.- natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably lower number of CD3.sup.-CD56.sup.-CD16.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+KIR2DL2/L3.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably lower number of CD3.sup.-CD56.sup.-NKp46.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+NKp30.sup.+ natural killer cells than an equivalent

number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+2B4.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; or a detectably higher number of CD3.sup.-CD56.sup.+CD94.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood.

10. The method of claim 1, wherein said natural killer cells have not been cultured prior to said administering.

11. A method of treating an individual having a viral infection, comprising administering to said individual isolated natural killer cells comprising isolated CD56.sup.+, CD16.sup.- placental intermediate natural killer cells.

12. The method of claim 11, wherein said natural killer cells are additionally CD3.sup.-.

13. The method of claim 11 additionally comprising administering to said individual an effective amount of lenalidomide, pomalidomide, or thalidomide.

14. The method of claim 11, wherein said isolated natural killer cells have been contacted with pomalidomide, lenalidomide, or thalidomide

prior to said administering.

15. The method of claim 11 wherein said natural killer cells comprise natural killer cells not obtained from placental perfusate.

16. The method of claim 11 wherein said natural killer cells are combined natural killer cells that comprise natural killer cells isolated from placental perfusate and natural killer cells isolated from umbilical cord blood.

17. The method of claim 16 wherein said umbilical cord blood is isolated from the placenta from which said placental perfusate is obtained.

18. The method of claim 13 wherein said natural killer cells are contacted with said pomalidomide, lenalidomide, or thalidomide in an amount and for a time sufficient for said natural killer cells to express detectably more granzyme B, or mRNA encoding granzyme B, than an equivalent number of natural killer cells not contacted with said pomalidomide, lenalidomide, or thalidomide.

19. The method of claim 16, wherein said combined natural killer cells comprise: a detectably higher number of CD3.sup.-CD56.sup.+CD16.sup.- natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably lower number of

CD3.sup.-CD56.sup.-CD16.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+KIR2DL2/L3.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably lower number of CD3.sup.-CD56.sup.-NKp46.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+NKp30.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+2B4.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; or a detectably higher number of CD3.sup.-CD56.sup.+CD94.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood.

20. The method of claim 11, wherein said natural killer cells have not been cultured prior to said administering.

21. A method of treating an individual having multiple myeloma, comprising administering to the individual (1) lenalidomide; (2) melphalan; and (3) expanded NK cells, wherein said NK cells are effective to treat multiple myeloma in said individual.

22. The method of claim 21, wherein said NK cells are umbilical cord NK

cells.

23. The method of claim 21, wherein said NK cells have been expanded for at least 14 days prior to said administering.

24. The method of claim 23, wherein said NK cells have been expanded for 14 days prior to said administering.

25. The method of claim 21, wherein said lenalidomide, melphalan, and expanded NK cells are administered to said individual separately.

26. A method of treating an individual having chronic lymphocytic leukemia (CLL), comprising administering to the individual (1) lenalidomide; (2) melphalan; (3) fludarabine; and (4) expanded NK cells, wherein said NK cells are effective to treat said CLL in said individual.

27. The method of claim 26, wherein said NK cells are umbilical cord NK cells.

28. The method of claim 26, wherein said NK cells have been expanded for at least 10 days prior to said administering.

29. The method of claim 28, wherein said NK cells have been expanded for

10 days prior to said administering.

30. The method of claim 26, wherein said lenalidomide, melphalan, fludarabine, and expanded NK cells are administered to said individual separately.

L25 ANSWER 3 OF 24 USPATFULL on STN

PI US 20110275672 A1 20111110

CLM What is claimed is:

1-32. (canceled)

33. A method of treating a blood-borne tumor, which comprises administering to a patient having the blood-borne tumor a therapeutically effective amount of a hydrated crystalline form of 3-(4-amino-l-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

34. The method of claim 33, wherein the crystalline form is a hemihydrate.

35. The method of claim 34, wherein the crystalline form has an X-ray powder diffraction pattern comprising peaks at approximately 16, 22 and 27 degrees 2.theta..

36. The method of claim 35, wherein the X-ray powder diffraction pattern further comprises a peak at approximately 18 degrees 2.theta..

37. The method of claim 34, wherein the crystalline form has differential scanning calorimetry thermogram comprising endotherms with maxima at about 146- C. and about 268- C.

38. The method of claim 34, wherein the crystalline form exhibits a mass loss of about 3.1% of its total mass when heated to about 175- C.

39. The method of claim 34, wherein the blood-borne tumor is myeloma, lymphoma, or leukemia.

40. The method of claim 39, wherein the myeloma is multiple myeloma, smoldering myeloma, or indolent myeloma.

41. The method of claim 40, wherein the multiple myeloma is relapsed multiple myeloma, refractory multiple myeloma, or newly diagnosed multiple myeloma.

42. The method of claim 39, wherein the lymphoma is non-Hodgkin's lymphoma, Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous

B-Cell lymphoma, diffuse large B-Cell lymphoma, or low grade follicular lymphoma.

43. The method of claim 39, wherein the lymphoma is non-Hodgkin's lymphoma.

44. The method of claim 39, wherein the leukemia is myeloblastic leukemia or myelogenous leukemia.

45. The method of claim 34, wherein the therapeutically effective amount is about 5 mg, 10 mg, 15 mg, or 25 mg.

46. The method of claim 34, wherein the crystalline form is administered orally.

47. The method of claim 34, wherein the crystalline form is administered in a capsule.

48. The method of claim 34, wherein the crystalline form is administered in a tablet.

49. The method of claim 34, wherein the crystalline form is substantially pure.

50. The method of claim 33, wherein the crystalline form has an X-ray powder diffraction pattern comprising peaks at approximately 27 and 28 degrees 2.theta..

51. The method of claim 50, wherein the crystalline form has a differential scanning calorimetry curve comprising endotherms with maxima at about 122- C. and about 270- C.

52. The method of claim 50, wherein the blood-borne tumor is myeloma, lymphoma, or leukemia.

53. The method of claim 52, wherein the myeloma is multiple myeloma, smoldering myeloma, or indolent myeloma.

54. The method of claim 53, wherein the multiple myeloma is relapsed multiple myeloma, refractory multiple myeloma, or newly diagnosed multiple myeloma.

55. The method of claim 52, wherein the lymphoma is non-Hodgkin's

lymphoma, Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, or low grade follicular lymphoma.

56. The method of claim 52, wherein the lymphoma is non-Hodgkin's lymphoma.

57. The method of claim 52, wherein the leukemia is myeloblastic leukemia or myelogenous leukemia.

58. The method of claim 50, wherein the therapeutically effective amount is about 5 mg, 10 mg, 15 mg, or 25 mg.

59. The method of claim 50, wherein the crystalline form is administered orally.

60. The method of claim 50, wherein the crystalline form is administered in capsule.

61. The method of claim 50, wherein the crystalline form is administered

in a tablet.

62. The method of claim 50, wherein the crystalline form is substantially pure.

L25 ANSWER 4 OF 24 USPATFULL on STN

PI US 20110236428 A1 20110929

CLM What is claimed is:

1. A method for treating cancer, comprising administering a peptide epoxyketone proteasome inhibitor or a pharmaceutically acceptable salt thereof; and one or more other therapeutic agents, wherein the combination shows efficacy that is greater than the efficacy of either agent being administered alone.

2. A method of claim 1, wherein the peptide epoxyketone has a structure of Formula (2), or a pharmaceutically acceptable salt thereof, ##STR24## wherein each A is independently selected from C.dbd.O, C.dbd.S, and SO.sub.2; or A is optionally a covalent bond when adjacent to an occurrence of Z; L is absent or is selected from C.dbd.O, C.dbd.S, and SO.sub.2; M is absent or is C.sub.1-12alkyl; Q is absent or is selected from O, NH, and N--C.sub.1-6alkyl; X is O; Y is absent or is

selected from O, NH, N--C.sub.1-6alkyl, S, SO, SO.sub.2, CHOR.sup.10, and CHCO.sub.2R.sup.10; each Z is independently selected from O, S, NH, and N--C.sub.1-6alkyl; or Z is optionally a covalent bond when adjacent to an occurrence of A; R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are each independently selected from optionally substituted C.sub.1-6alkyl, C.sub.1-6hydroxyalkyl, C.sub.1-6alkoxyalkyl, aryl, and C.sub.1-6aralkyl;

R.sup.5 is N(R.sup.6)LQR.sup.7; R.sup.6, R.sup.12, R.sup.13, and R.sup.14 are independently selected from hydrogen, OH, and C.sub.1-6alkyl; R.sup.7 is selected from hydrogen, C.sub.1-6alkyl, C.sub.1-6alkenyl, C.sub.1-6alkynyl, aryl, C.sub.1-6aralkyl, heteroaryl, C.sub.1-6heteroaralkyl, R.sup.8ZAZ--C.sub.1-6alkyl-, R.sup.11Z--C.sub.1-8alkyl-, (R.sup.80)(R.sup.90)P(.dbd.O)O--C.sub.1-8alkyl-ZAZ--C.sub.1-8alkyl-, R.sup.8ZAZ--C.sub.1-8alkyl-ZAZ--C.sub.1-8alkyl-, heterocyclylMZAZ--C.sub.1-8alkyl-, (R.sup.80)(R.sup.90)P(.dbd.O)O--C.sub.1-8alkyl-, (R.sup.10).sub.2N--C.sub.1-12alkyl-, (R.sup.10).sub.3N--C.sub.1-12alkyl-, heterocyclylM-, carbocyclylM-, R.sup.11SO.sub.2C.sub.1-8alkyl-, and R.sup.11SO.sub.2NH; or R.sup.6 and R.sup.7 together are C.sub.1-6alkyl-Y--C.sub.1-6alkyl, C.sub.1-6alkyl-ZAZ--C.sub.1-6alkyl, ZAZ--C.sub.1-6alkyl-ZAZ--C.sub.1-6alkyl, ZAZ--C.sub.1-6alkyl-ZAZ, or C.sub.1-6alkyl-A, thereby forming a ring; R.sup.8 and R.sup.9 are

independently selected from hydrogen, metal cation, C.sub.1-6alkyl, C.sub.1-6alkenyl, C.sub.1-6alkynyl, aryl, heteroaryl, C.sub.1-6aralkyl, and C.sub.1-6heteroaralkyl; each R.sup.10 is independently selected from hydrogen and C.sub.1-6alkyl; R.sup.11 is independently selected from hydrogen, C.sub.1-6alkyl, C.sub.1-6alkenyl, C.sub.1-6alkynyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, C.sub.1-6aralkyl, and C.sub.1-6heteroaralkyl, R.sup.15 and R.sup.16 are independently selected from hydrogen and C.sub.1-6alkyl, or R.sup.15 and R.sup.16 together form a 3- to 6-membered carbocyclic or heterocyclic ring; and R.sup.17 and R.sup.18 are independently selected from hydrogen, a metal cation, C.sub.1-6alkyl, and C.sub.1-6aralkyl, or R.sup.17 and R.sup.18 together represent C.sub.1-6alkyl, thereby forming a ring; provided that when R.sup.6, R.sup.12, R.sup.13, and R.sup.14 are H or CH.sub.3, and Q is absent, LR.sup.7 is not hydrogen, unsubstituted C.sub.1-6alkylC.dbd.O, a further chain of amino acids, t-butoxycarbonyl (Boc), benzoyl (Bz), fluoren-9-ylmethoxycarbonyl (Fmoc), triphenylmethyl(trityl), benzyloxycarbonyl (Cbz), trichloroethoxycarbonyl (Troc); or substituted or unsubstituted aryl or heteroaryl; and in any occurrence of the sequence ZAZ, at least one member of the sequence must be other than a covalent bond.

3. A method of claim 1, wherein the peptide epoxyketone has a structure of Formula (4), or a pharmaceutically acceptable salt thereof,

##STR25## wherein each A is independently selected from C.dbd.O, C.dbd.S, and SO.sub.2; or A is optionally a covalent bond when adjacent to an occurrence of Z; L is absent or is selected from C.dbd.O, C.dbd.S, and SO.sub.2; M is absent or is C.sub.1-12alkyl; Q is absent or is selected from O, NH, and N--C.sub.1-6alkyl; X is O; Y is absent or is selected from O, NH, N--C.sub.1-6alkyl, S, SO, SO.sub.2, CHOR.sup.10, and CHCO.sub.2R.sup.10; each Z is independently selected from O, S, NH, and N--C.sub.1-6alkyl; or Z is optionally a covalent bond when adjacent to an occurrence of A; R.sup.2 and R.sup.4 are each independently selected from optionally substituted C.sub.1-6alkyl, C.sub.1-6hydroxyalkyl, C.sub.1-6alkoxyalkyl, aryl, and C.sub.1-6aralkyl;

R.sup.5 is N(R.sup.6)LQR.sup.7; R.sup.6 is selected from hydrogen, OH, and C.sub.1-6alkyl, preferably C.sub.1-6alkyl; R.sup.7 is selected from hydrogen, C.sub.1-6alkyl, C.sub.1-6alkenyl, C.sub.1-6alkynyl, aryl, C.sub.1-6aralkyl, heteroaryl, C.sub.1-6heteroaralkyl, R.sup.8ZAZ--C.sub.1-8alkyl-, R.sup.11Z--C.sub.1-8alkyl-, (R.sup.80)(R.sup.90)P(.dbd.O)O--C.sub.1-8alkyl-ZAZ--C.sub.1-8alkyl-, R.sup.8ZAZ--C.sub.1-8alkyl-ZAZ--C.sub.1-8alkyl-,

heterocyclylMZAZ--C.sub.1-8alkyl-,

(R.sup.80)(R.sup.90)P(.dbd.O)O--C.sub.1-8alkyl-,

(R.sup.10).sub.2N--C.sub.1-12alkyl-,

(R.sup.10).sub.3N--C.sub.1-12alkyl-, heterocyclylM-, carbocyclylM-,

R.sup.11SO.sub.2C.sub.1-8alkyl-, and R.sup.11SO.sub.2NH; or R.sup.6 and

R.sup.7 together are C.sub.1-6alkyl-Y--C.sub.1-6alkyl,

C.sub.1-6alkyl-ZAZ--C.sub.1-6alkyl,

ZAZ--C.sub.1-6alkyl-ZAZ--C.sub.1-6alkyl, ZAZ--C.sub.1-6alkyl-ZAZ, or

C.sub.1-6alkyl-A, thereby forming a ring; R.sup.8 and R.sup.9 are

independently selected from hydrogen, metal cation, C.sub.1-6alkyl,

C.sub.1-6alkenyl, C.sub.1-6alkynyl, aryl, heteroaryl, C.sub.1-6aralkyl,

and C.sub.1-6heteroaralkyl; each R.sup.10 is independently selected
from

hydrogen and C.sub.1-6alkyl; and R.sup.11 is independently selected
from

hydrogen, C.sub.1-6alkyl, C.sub.1-6alkenyl, C.sub.1-6alkynyl,

carbocyclyl, heterocyclyl, aryl, heteroaryl, C.sub.1-6aralkyl, and

C.sub.1-6heteroaralkyl, provided that when R.sup.6 is H or CH.sub.3 and

Q is absent, LR.sup.7 is not hydrogen, unsubstituted

C.sub.1-6alkylC.dbd.O, a further chain of amino acids, t-butoxycarbonyl

(Boc), benzoyl (Bz), fluoren-9-ylmethoxycarbonyl (Fmoc),

triphenylmethyl(trityl), benzyloxycarbonyl (Cbz),

trichloroethoxycarbonyl (Troc); or substituted or unsubstituted aryl or

heteroaryl; and in any occurrence of the sequence ZAZ, at least one member of the sequence must be other than a covalent bond.

4. A method of claim 1, wherein the peptide epoxyketone has a structure of Formula (10), or a pharmaceutically acceptable salt thereof, ##STR26## wherein L is absent or is selected from --CO.sub.2 or --C(.dbd.S)O; X is O; Y is NH, N-alkyl, O, or C(R.sup.9).sub.2; Z is O or C(R.sup.9).sub.2; R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are all hydrogen; each R.sup.5, R.sup.6, R.sup.7, R.sup.8, and R.sup.9 is independently selected from hydrogen and optionally substituted C.sub.1-6alkyl, C.sub.1-6hydroxyalkyl, C.sub.1-6alkoxyalkyl, aryl, and C.sub.1-6aralkyl, wherein substituents may include, but are not limited to, alkyl, amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether; R.sup.10 and R.sup.11 are independently selected from hydrogen and C.sub.1-6alkyl, or R.sup.10 and R.sup.11 together form a 3- to 6-membered carbocyclic or heterocyclic ring; R.sup.12 and R.sup.13 are independently selected from hydrogen, a metal cation, C.sub.1-6alkyl, and C.sub.1-6aralkyl, or R.sup.12 and R.sup.13 together represent C.sub.1-6alkyl, thereby forming a ring; m is an integer from 0 to 2; and

n is an integer from 0 to 2.

5. A method of claim 1, wherein the peptide epoxyketone has a structure of Formula (12), or a pharmaceutically acceptable salt thereof,

##STR27## where X is O; R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are all hydrogen; and R.sup.5, R.sup.6, R.sup.7, and R.sup.8 are independently selected from hydrogen and optionally substituted C.sub.1-6alkyl, C.sub.1-6hydroxyalkyl, C.sub.1-6alkoxyalkyl, aryl, and C.sub.1-6aralkyl,

wherein substituents may include, but are not limited to, amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether.

6. A method of claim 1, wherein the peptide epoxyketone has the following structure, or a pharmaceutically acceptable salt thereof:

##STR28##

7. A method of claim 1, wherein the effects of the peptide epoxyketone and the one or more other therapeutic agents are synergistic.

8. A method of claim 1, wherein the effects of the peptide epoxyketone and the one or more other therapeutic agents are additive.

9. A method of claim 1, wherein the peptide epoxyketone and the one or more other therapeutic agents are administered simultaneously.

10. A method of claim 1, wherein the one or more other therapeutic agents are administered within about 5 minutes to within about 48 hours prior to or after administration of the peptide epoxyketone.

11. A method of claim 10, wherein the one or more other therapeutic agents are administered within about 5 minutes to within about 1 hour prior to or after administration of the peptide epoxyketone.

12. A method of claim 1, wherein the cancer is selected from hematological malignancies, solid tumors, neuroblastoma, or melanoma.

13. A method of claim 12, wherein the cancer is selected from mantle cell lymphoma, diffuse large B-cell lymphoma (DLBCL), T-cell lymphomas or leukemias (e.g., cutaneous T-cell lymphoma (CTCL), noncutaneous peripheral T-cell lymphoma, lymphoma associated with human T-cell lymphotrophic virus (HTLV), and adult T-cell leukemia/lymphoma (ATLL)), acute lymphocytic leukemia, acute myelogenous leukemia (e.g., acute monocytic leukemia and acute promyelocytic leukemia), chronic lymphocytic leukemia (e.g., chronic B cell leukemia), chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma (e.g., Burkitt's lymphoma), myeloma, multiple myeloma, and myelodysplastic syndrome.

14. A method of claim 12, wherein the cancer is selected from multiple myeloma and lymphoma.

15. A method of claim 12, wherein the cancer is selected from mesothelioma, brain neuroblastoma, retinoblastoma, glioma, Wilms' tumor, bone cancer and soft-tissue sarcomas, head and neck cancers (e.g., oral, laryngeal and esophageal), genitourinary cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular, rectal, and colon), lung cancer (e.g., small cell carcinoma and non-small cell lung carcinoma, including squamous cell carcinoma and adenocarcinoma), breast cancer, pancreatic cancer, basal cell carcinoma, metastatic skin carcinoma, squamous cell carcinoma (both ulcerating and papillary type), stomach cancer, brain cancer, liver cancer, adrenal cancer, kidney cancer, thyroid cancer, medullary carcinoma, osteosarcoma, soft-tissue sarcoma, Ewing's sarcoma, reticulum cell sarcoma, and Kaposi's sarcoma.

16. A method of claim 15, wherein the cancer is selected from ovarian cancer, non-small cell lung cancer, and colorectal cancer.

17. A method of claim 1, wherein the other therapeutic agent is an HDAC

inhibitor.

18. A method of claim 17, wherein the HDAC inhibitor is selected from trichostatin A, depsipeptide, apicidin, A-161906, scriptaid, PXD-101, CHAP, butyric acid, depudecin, oxamflatin, phenylbutyrate, valproic acid, SAHA (Vorinostat), MS275 (N-(2-Aminophenyl)-4-[N-(pyridine-3-ylmethoxy-carbonyl)aminomethyl]benzamide), LAQ824/LBH589, C1994, and MGCD0103.

19. A method of claim 18, wherein the HDAC inhibitor is SAHA.

20. A method of claim 1, wherein the other therapeutic agent is an antibiotic.

21. A method of claim 20, wherein the antibiotic is selected from dactinomycin (actinomycin D), daunorubicin, doxorubicin and idarubicin.

22. A method of claim 21, wherein the antibiotic comprises doxorubicin.

23. A method of claim 1, wherein the other therapeutic agent is a taxane.

24. A method of claim 23, wherein the taxane is selected from

paclitaxel

and docetaxel.

25. A method of claim 1, wherein the other therapeutic agent is an antiproliferative/antimitotic alkylating agents.

26. A method of claim 25, wherein the antiproliferative/antimitotic alkylating agent is a nitrogen mustard.

27. A method of claim 26, wherein the nitrogen mustard is selected from mechlorethamine, ifosphamide, cyclophosphamide and analogs, melphalan, and chlorambucil.

28. A method of claim 1, wherein the other therapeutic agent is a platinum coordination complex.

29. A method of claim 28, wherein the platinum coordination complex is selected from cisplatin and carboplatin.

30. A method of claim 1, wherein the other therapeutic agent is a steroid.

31. A method of claim 30, wherein the steroid is selected from

hydrocortisone, dexamethasone, methylprednisolone and prednisolone.

32. A method of claim 31, wherein the steroid is dexamethasone.

33. A method of claim 1, wherein the other therapeutic agent is an immunomodulator.

34. A method of claim 33, wherein the immunomodulator is selected from thalidomide, CC-4047 (Actimid), and lenalidomide (Revlimid).

35. A method of claim 34, wherein the immunomodulator is lenalidomide.

36. A method of claim 1, wherein the other therapeutic agent is a topoisomerase inhibitor.

37. A method of claim 36, wherein the topoisomerase inhibitor is selected from irinotecan, topotecan, camptothecin, lamellarin D, and etoposide.

38. A method of claim 1, wherein the other therapeutic agent is an m-TOR inhibitor.

39. A method of claim 38, wherein the m-TOR inhibitor is selected from CCI-779, AP23573 and RAD-001.

40. A method of claim 1, wherein the other therapeutic agent is a protein kinase inhibitor.

41. A method of claim 40, wherein the protein kinase inhibitor is selected from sorafenib, imatinib, dasatinib, sunitinib, pazopanib, and nilotinib.

42. A method of claim 41, wherein the protein kinase inhibitor is sorafenib.

43. A method for treating autoimmune diseases, comprising administering a peptide epoxyketone or a pharmaceutically acceptable salt thereof; and

one or more other therapeutic agents, wherein the combination shows efficacy that is greater than the efficacy of either agent being administered alone.

L25 ANSWER 5 OF 24 USPATFULL on STN

PI US 20110123486 A1 20110526

CLM What is claimed is:

1. A method of treating a resistant cancer, comprising administering to a patient a therapeutically effective amount of an erastin analog.

2. The method of claim 1, wherein the cancer is resistant to one or more of dexamethasone, alkylators, anthracyclines (e.g., doxorubicin), lenalidomide, CC-4047, bortezomib, and multitargeted kinase inhibitors.

3. The method of claim 1 or 2, wherein the cancer is multiple myeloma.

4. A method of treating leiomyosarcoma, fibrosarcoma or mesenchymal chondrosarcoma, comprising administering to a patient a therapeutically effective amount of an erastin analog.

5. A method of treating multiple myeloma characterized by a cell type selected from one or more OPM-2 cells, OPM-2-like cells, MM-IS cells, MM-IS-like cells, MM.1R cells, MM-1R-like cells, KMS-18 cells, KMS-18-like cells, S6B45 cells, S6B45-like cells, MR20 cells, MR20-like cells, ARD cells and/or ARD-like cells, comprising administering to a patient a therapeutically effective amount of an erastin analog.

6. A method of inhibiting cell growth, wherein the cell is selected

from

A-549, NCI-H1734, Calu-1, A-427, Calu-6, DLD-1, OVCAR-5, HS766T, CFPAC-1, Capan-2, HT-29, CCD841, SK-MEL-2, SU.86.86, COLO-205, AsPC-1, HUVEC, BxPC-3, and Capan-1 cells, comprising contacting the cells with an effective amount of erastin analog.

7. The method of claim 1, wherein the erastin analog is a compound represented by structural formula (I): ##STR70## wherein: R.sup.1 is selected from H, --Z-Q-Z, --C.sub.1-8alkyl-N(R.sup.2)(R.sup.4), --C.sub.1-8alkyl-OR.sup.3, 3- to 8-membered carbocyclic or heterocyclic, aryl, heteroaryl, and C.sub.1-4aralkyl; R.sup.2 and R.sup.4 are each independently for each occurrence selected from H, C.sub.1-4alkyl, C.sub.1-4aralkyl, aryl, heteroaryl, acyl, alkylsulfonyl, and arylsulfonyl, provided that when both R.sup.2 and R.sup.4 are on the same N and either R.sup.2 and R.sup.4 is acyl, alkylsulfonyl, or arylsulfonyl, then the other is selected from H, C.sub.1-8alkyl, aryl, C.sub.1-4aralkyl, and heteroaryl; R.sup.3 is selected from H, C.sub.1-4alkyl, C.sub.1-4aralkyl, aryl and heteroaryl; W is selected from ##STR71## Q is slected from O and NR.sup.2; and Z is independently for each occurrence selected from C.sub.1-6alkyl, C.sub.2-6alkenyl, and C.sub.2-6alkynyl.

8. The method of claim 7, wherein the compound is represented by the following formula: ##STR72##

9. The method of claim 1, wherein the erastin analog is a compound represented by Structural Formula (VI): ##STR73## or a pharmaceutically acceptable salt thereof, where: Ring A is optionally substituted; W is absent or is selected from C, N, S and O; X, Y and Z are selected from C, N, S and O, wehre at least one of X, Y and Z is N if W is C; Ar is an optionally substituted phenyl group; R.sub.4 and R.sub.5 are independently selected from --H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted non-aromatic heterocyclic and substituted or unsubstituted aryl, where alkyl, alkenyl and alkynyl are optionally interrupted by NR, O or S(O).sub.n; or R.sub.4 and R.sub.5 taken together form a 3- to 8-membered carbocyclic or heterocyclic group; V is --NH-L-A-Q or ##STR74## Ring C is a substituted or unsubstituted heterocyclic aromatic or non-aromatic ring;

A is NR or O; or A is a covalent bond; L is a substituted or unsubstituted hydrocarbyl group optionally interrupted by one or more heteroatoms selected from N, O and S; Q is selected from --R, --C(O)R', --C(O)N(R).sub.2, --C(O)OR' and --S(O).sub.2R'; each R is independently

--H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl or substituted or unsubstituted non-aromatic heterocyclic; each R' is independently a substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl group, substituted or unsubstituted non-aromatic herterocyclic or substituted or unsubstituted aryl group; and each n is independently 0, 1 or 2.

10. The method of claim 1, wherein the erastin analog is compound represented by Structural Formula (X): ##STR75## or a pharmaceutically

acceptable salt thereof where: R.sub.a is a halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl-O--, substituted or unsubstituted alkyl-O--, substituted or unsubstituted alkenyl-O-- or substituted or unsubstituted alkynyl-O--, where alkyl, alkenyl and alkynyl are optionally interrupted by NR, O or S(O).sub.n; each R.sub.2 is independently selected from halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted non-aromatic heterocyclic, --CN, --COOR', --CON(R).sub.2, --NRC(O)R, --SO.sub.2N(R).sub.2, --N(R).sub.2, --NO.sub.2, --OH and --OR'; each R.sub.3 is independently selected from halogen, substituted

or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted non-aromatic heterocyclic, --CN, --COOR', --CON(R).sub.2, --NRC(O)R, --SO.sub.2N(R).sub.2, --N(R).sub.2, --NO.sub.2, --OH and --OR'; R.sub.4 and R.sub.5 are independently selected from --H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted non-aromatic heterocyclic and substituted or unsubstituted aryl, where alkyl, alkenyl and alkynyl are optionally interrupted by NR, O or S(O).sub.n; or R.sub.4 and R.sub.5 taken together form a carbocyclic or heterocyclic group; V is --NH-L-A-Q or ##STR76## Ring C is a substituted or unsubstituted heterocyclic aromatic or non-aromatic ring; A is NR or O; or A is a covalent bond; L is a substituted or unsubstituted hydrocarbyl group optionally interrupted by one or more heteroatoms selected from N, O and S; Q is selected from --R, --C(O)R', --C(O)N(R).sub.2, --C(O)OR' and --S(O).sub.2R'; each R is independently --H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl or substituted or unsubstituted non-aromatic heterocyclic; each R' is independently a substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl group, substituted or unsubstituted non-aromatic heterocyclic or substituted

or

unsubstituted aryl group; j is an interger from 0 to 4; k is an interger

from 0 to 4, provided that at least one of j and k is an interger from 1

to 4; and each n is independently 0, 1 or 2.

11. The method of claim 1, further comprising conjointly administering to said patient an agent that kills cells through an apoptotic mechanism.

12. The method of claim 11, wherein said agent is a chemotherapeutic agent.

13. The method of claim 12, wherein said chemotherapeutice agent is selected from: an EGF-receoptor antagonist, arsenic sulfide, adriamycin, cisplatin, carboplatin, cimetidine, caminomycin, mechlorethamine hydrochloride, pentamethylmelamine, thiotepa, teniposide, cyclophosphamide, chlorambucil, demethoxyhypocrellin A, melphalan, ifosfamide, trofosfamide, Treosulfan, podophyllotoxin or podophyllotoxin derivatives, etoposide phosphate, teniposide, etoposide, leurosidine, leurosine, vindesine, 9-aminocamptothecin, camptoirinotecan, crisnatol,

megestrol, methopterin, mitomycin C, ecteinascidin 743, busulfan, carmustine, lomustine, lovastatin, 1-methyl-4-phenylpyridinium ion, semustine, staurosporine, streptozocin, phthalocyanine, dacarbazine, aminopterin, methotrexate, trimetrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, porfiromycin, 5-fluorouracil, 6-mercaptopurine, doxorubicin hydrochloride, leucovorin, mycophenolic acid, daunorubicin, deferoxamine, floxuridine, doxifluridine, raltitrexed, idarubicin, epirubican, pirarubican, zorubicin, mitoxantrone, bleomycin sulfate, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, vertoporfin, paclitaxel, tamoxifen, raloxifene, tiazofuran, thioguanine, ribavirin, EICAR, estramustine, estramustine phosphate sodium, flutamide, bicalutamide, buserelin, leuprolide, pteridines, enediynes, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, betamethasone, gemcitabine hydrochloride, verapamil, VP-16, altretamine, thapsigargin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, DCP, PLD-147, JM118, JM216, JM335, satraplatin, docetaxel, deoxygenated paclitaxel, TL-139, 5'-nor-anhydrovinblastine, camptothecin, irinotecan, topotecan, BAY 38-3441, 9-nitrocamptothecin, exatecan, lurtotecan, gimatecan, homocamptothecins diflomotecan and 9-aminocamptothecin,

SN-38, ST 1481, karanitecin, indolocarbazoles, protoberberines, intoplicines, idenoisoquinolones, benzo-phenazines and NB-506.

14. A pharmaceutical composition comprising a compound represented by the following formula: ##STR77## or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is suitable for intravenous administration.

15. The pharmaceutical composition of claim 14, wherein the compound is a pharmaceutically acceptable salt.

16. The pharmaceutical composition of claim 15, wherein the compound is the dihydrochloride salt.

L25 ANSWER 6 OF 24 USPATFULL on STN

PI US 20100093683 A1 20100415

CLM What is claimed is:

1-21. (canceled)

22. A method of treating multiple myeloma, which comprises cyclically administering to a patient having multiple myeloma about 5 to about 50 mg per day of a compound of the formula: ##STR9## or a

pharmaceutically acceptable salt, or stereoisomer thereof, and a therapeutically effective amount of a proteasome inhibitor.

23. The method of claim 22, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

24. The method of claim 22, wherein the compound is a pharmaceutically acceptable salt.

25. The method of claim 22, wherein the compound is a pharmaceutically acceptable stereoisomer.

26. The method of claim 25, wherein the stereoisomer is an enantiomerically pure R isomer.

27. The method of claim 25, wherein the stereoisomer is an enantiomerically pure S isomer.

28. The method of claim 22, which further comprises administering a therapeutically effective amount of an additional active agent.

29. The method of claim 28, wherein the additional active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

30. The method of claim 29, wherein the additional active agent is dexamethasone.

31. The method of claim 28, wherein the additional active agent is melphalan, doxorubicin, vincristine, prednisone, cyclophosphamide, dexamethasone, biaxin, or a combination thereof.

32. The method of claim 22, which further comprises bone marrow transplantation, autologous stem cell transplantation, radiation therapy, hormonal therapy, biological therapy or immunotherapy.

33. The method of claim 22, wherein the multiple myeloma is relapsed, refractory or resistant to conventional therapy.

34. The method of claim 22, wherein the compound is administered orally.

35. The method of claim 34, wherein the compound is administered in the form of a capsule or tablet.

36. The method of claim 22, wherein the compound is administered in an amount of from about 5 to about 25 mg per day.

37. The method of claim 30, wherein the compound is administered in an amount of about 5, 10, 15, 20, 25 or 30 mg per day.

38. The method of claim 22, wherein the compound is administered to a patient having previously untreated multiple myeloma.

39. The method of claim 36, wherein the compound is administered in an amount of about 25 mg per day.

40. The method of claim 22, wherein one cycle comprises three to six weeks.

41. The method of claim 22, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

42. The method of claim 22, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

43. The method of claim 22, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days every 28

days.

44. The method of claim 22, wherein the compound is administered in an amount of from about 5 to about 15 mg per day for days 1-14 every 21 days for eight cycles.

45. The method of claim 22, wherein the compound is administered in an amount of about 5 to about 25 mg per day and dexamethasone is administered in an amount of about 40 mg per day on days 1-4 every four to six weeks.

46. The method of claim 22, wherein the compound is administered in an amount of 15 mg per day.

47. The method of claim 36, wherein the compound is administered in an amount of 10 mg per day.

48. The method of claim 22, wherein the compound is administered in a capsule of 5 mg, 10 mg, 15 mg or 25 mg.

49. The method of claim 22, wherein the compound is ##STR10##

50. A method of treating multiple myeloma, which comprises cyclically

administering to a patient having multiple myeloma: (a) about 5 to about 25 mg per day of a compound of the formula: ##STR11## (b) a therapeutically effective amount of a proteasome inhibitor, and (c) a therapeutically effective amount of dexamethasone.

51. The method of claim 22, wherein the compound is administered in an amount of about 15 mg twice a day.

52. The method of claim 22, which further comprises administering a therapeutically effective amount of doxorubicin.

53. The method of claim 22, which further comprises administering a therapeutically effective amount of melphalan.

54. The method of claim 48, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

55. A method of treating multiple myeloma using which comprises cyclically administering to a patient having multiple myeloma; (a) for 14 consecutive days about 15 mg per day of a compound of the formula: ##STR12## followed by seven consecutive days of rest, (b) a

therapeutically effective amount of a proteasome inhibitor, and (c) a therapeutically effective amount of dexamethasone.

L25 ANSWER 7 OF 24 USPATFULL on STN

PI US 20100092489 A1 20100415

CLM What is claimed is:

1. A method for inhibiting growth and/or proliferation of tumor cells expressing CD38 in an individual in need thereof, which method comprises

administration to the said individual of i) a non-agonistic antibody which binds to CD38, ii) at least one corticosteroid, and iii) at least one non-corticosteroid chemotherapeutic agent.

2. A method for treating cancer involving tumor cells expressing CD38 in

an individual in need thereof, which method comprises administration to the said individual of: i) a non-agonistic antibody which binds to CD38,

ii) optionally at least one corticosteroid, and iii) optionally at least

one non-corticosteroid chemotherapeutic agent, followed by autologous peripheral stem cell or bone marrow transplantation.

3. The method of claim 1, wherein said at least one non-corticosteroid chemotherapeutic agent comprises a cytotoxic agent and/or an angiogenesis inhibitor.

4. The method of claim 1, wherein said at least one non-corticosteroid chemotherapeutic agent comprises an alkylating agent.

5. The method of claim 1, wherein said at least one non-corticosteroid chemotherapeutic agent comprises one or more agents selected from the group consisting of: melphalan, mechlorethamine, thioepa, chlorambucil, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, dacarbazine (DTIC), procarbazine, mitomycin C, cisplatin and other platinum derivatives, such as carboplatin.

6. The method of claim 1, wherein said at least one non-corticosteroid chemotherapeutic agent comprises a glutamic acid derivative, such as thalidomide (Thalomid®) or a thalidomide analog, e.g. CC-5013 (lenalidomide, Revlimid.TM.) or CC4047 (Actimid.TM.).

7. The method of claim 1, wherein said at least one non-corticosteroid chemotherapeutic agent comprises a proteasome inhibitor, such as bortezomib (Velcade®).

8. The method of claim 1, wherein said at least one non-corticosteroid chemotherapeutic agent comprises a vinca alkaloid, such as vincristine.

9. The method of claim 1 wherein said at least one non-corticosteroid chemotherapeutic agent comprises an anthracycline, such as doxorubicin.

10. The method of claim 1, wherein said at least one corticosteroid comprises a glucocorticoid.

11. The method of claim 1, wherein said at least one corticosteroid comprises prednisone.

12. The method of claim 1, wherein said at least one corticosteroid comprises prednisone and said at least one non-corticosteroid chemotherapeutic agent comprises melphalan.

13. The method of claim 1, wherein said at least one corticosteroid comprises prednisone and said at least one non-corticosteroid chemotherapeutic agent comprises thalidomide.

14. The method of claim 1, wherein said at least one corticosteroid comprises prednisone and said at least one non-corticosteroid

chemotherapeutic agent comprises melphalan and thalidomide.

15. The method of claim 1, wherein said at least one corticosteroid comprises dexamethasone.

16. The method of claim 1, wherein said at least one corticosteroid comprises dexamethasone and said at least one non-corticosteroid chemotherapeutic agent comprises thalidomide and/or lenalidomide.

17. The method of claim 1, wherein said at least one corticosteroid comprises dexamethasone and said at least one non-corticosteroid chemotherapeutic agent comprises vincristine and/or doxorubicin.

18. The method of claim 1, comprising the further administration of interferon-alpha.

19. The method of claim 1, wherein said antibody is a monoclonal antibody.

20. The method of claim 1, wherein said antibody is a human monoclonal antibody.

21. The method of claim 1, wherein said antibody is an antagonist of

CD38.

22. The method of claim 1, wherein said antibody is an antibody that does not induce release of significant IL-6 by human monocytes or peripheral blood mononuclear cells as determined by the method described in Example 19 of the specification.

23. The method of claim 1, wherein said antibody is an antibody that does not induce release of detectable IFN-.gamma. by human T cells or peripheral blood mononuclear cells as determined by the method described in Example 20 of the specification.

24. The method of claim 1, wherein said antibody is an antibody that is internalized by CD38 expressing cells; such as internalized by CHO-CD38 cells within 5 to 15 minutes at 37- C. by the method as described in Example 12 of the specification.

25. The method of claim 1, wherein said antibody is an antibody that induces ADCC; such as with an EC50 value of below 15 ng/ml, such as below 10 ng/ml in Daudi-luc cells and with an EC50 value of below 75 ng/ml, such as below 50 ng/ml, 30 ng/ml or 10 ng/ml in MM cells as

determined by the method described in Example 5 of the specification.

26. The method of claim 1, wherein said antibody is an antibody that induces CDC in the presence of complement; such as with an EC50 value of

below 5 .mu.g/ml, such as below 1 .mu.g/ml in daudi-luc or CD38-CHO cells by the method described in Example 6 of the specification.

27. The method of claim 1, wherein said antibody is an antibody that inhibits the synthesis of cGDPR.

28. The method of claim 1, wherein said antibody is an antibody that inhibits the synthesis of cADPR.

29. The method of claim 1, wherein said antibody is an antibody that binds to human CD38 with an affinity (KD) of below 10.sup.-8 M, such as in the range of from 10.sup.-8 M to 10.sup.-11 M, for example in the range of from 7.times.10.sup.-9 M to 10.sup.-10 M, as determined by surface plasmon resonance as described in Example 20 of the specification.

30. The method of claim 1, wherein said antibody is an antibody that inhibits the synthesis of cGDPR by at least 25%, such as at least 30%

after 90 minutes at a concentration of 3 .mu.g/ml as determined by spectophotometric method described in Example 24 of the specification.

31. The method of claim 1, wherein said antibody is an antibody that inhibits the synthesis of cADPR by at least 25%, such as at least 30% after 90 minutes at a concentration of 3 .mu.g/ml as determined by the HPLC method described in Munshi et al., J. Biol. Chem. 275, 21566-21571 (2000).

32. The method of claim 1, wherein said antibody is an antibody comprising a VH CDR3 having the sequence as set forth in SEQ ID No:10 or

an antibody which competes for CD38 binding with said antibody, e.g. by binding the same epitope as said antibody.

33. The method of claim 1, wherein said antibody is an antibody comprising a VL CDR3 having the sequence as set forth in SEQ ID No:5 and

a V H CDR3 having the sequence as set forth in SEQ ID No:10.

34. The method of claim 1, wherein said antibody is an antibody comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a VL CDR1 having the sequence as set forth in SEQ ID No:3, a V L CDR2 having the sequence as set

forth

in SEQ ID No:4 and a VL CDR3 having the sequence as set forth in SEQ ID No:5, and the heavy chain variable region comprises a VH CDR1 having the

sequence as set forth in SEQ ID No:8, a VH CDR2 having the sequence as set forth in SEQ ID No:9 and a VH CDR3 having the sequence as set forth in SEQ ID No:10.

35. The method of claim 32 wherein said antibody is an antibody comprising a VL region having the amino acid sequence as set forth in SEQ ID No:2 or a VL region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:2.

36. The method of claim 32, wherein said antibody is an antibody comprising a VH region having the amino acid sequence as set forth in SEQ ID No:7 or a VH region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:7 or a VH region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No:7.

37. The method of claim 1, wherein said antibody is an antibody

comprising a VH CDR3 having the sequence as set forth in SEQ ID No:20 or

an antibody which competes for CD38 binding with said antibody, e.g. by binding the same epitope as said antibody.

38. The method of claim 1, wherein said antibody is an antibody comprising a VL CDR3 having the sequence as set forth in SEQ ID No:15 and a VH CDR3 having the sequence as set forth in SEQ ID No:20.

39. The method of claim 1, wherein said antibody is an antibody comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a VL CDR1 having the sequence as set forth in SEQ ID No:13, a VL CDR2 having the sequence as set forth in SEQ ID No: 14 and a VL CDR3 having the sequence as set forth in SEQ ID No:15, and the heavy chain variable region comprises a VH CDR1 having the sequence as set forth in SEQ ID No: 18, a VH CDR2 having the sequence as set forth in SEQ ID No:19 and a VH CDR3 having the sequence as set forth in SEQ ID No:20.

40. The method of claim 37, wherein said antibody is an antibody comprising a VL region having the amino acid sequence as set forth in SEQ ID No:12 or a VL region having at least about 90%, such as at least

about 95% amino acid sequence identity to the sequence according to SEQ ID No:12.

41. The method of claim 37, wherein said antibody is an antibody comprising a VH region having the amino acid sequence as set forth in SEQ ID No: 17 or a VH region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:17 or a VH region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No: 17.

42. The method of claim 1, wherein said antibody is an antibody comprising a VH CDR3 having the sequence as set forth in SEQ ID No:30 or an antibody which competes for CD38 binding with said antibody, e.g. by binding the same epitope as said antibody.

43. The method of claim 1, wherein said antibody is an antibody comprising a VL CDR3 having the sequence as set forth in SEQ ID No:25 and a VH CDR3 having the sequence as set forth in SEQ ID No:30.

44. The method of claim 1, wherein said antibody is an antibody

comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a VL CDR1 having the sequence as set forth in SEQ ID No:23, a VL CDR2 having the sequence as set forth in SEQ ID No:24 and a VL CDR3 having the sequence as set forth in SEQ ID No:25, and the heavy chain variable region comprises a VH CDR1 having the sequence as set forth in SEQ ID No:28, a VH CDR2 having the sequence as set forth in SEQ ID No:29 and a VH CDR3 having the sequence as set forth in SEQ ID No:30.

45. The method of claim 42, wherein said antibody is an antibody comprising a VL region having the amino acid sequence as set forth in SEQ ID No:22 or a VL region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:22.

46. The method of claim 42, wherein said antibody is an antibody comprising a VH region having the amino acid sequence as set forth in SEQ ID No:27 or a VH region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:27 or a VH region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set

forth in SEQ ID No:27.

47. The method of claim 1, wherein said antibody is a full length IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody, such as an IgG1 antibody, preferably an IgG1,.kappa. antibody or an IgM antibody, preferably an IgM,.kappa. antibody.

48. The method of claim 1, wherein said antibody is a human monoclonal antibody comprising (i) a heavy chain variable region amino acid sequence derived from a human Hv1263/3M28 (VHI) germline sequence and a light chain variable region amino acid sequence derived from a human L15

(VKI) germline sequence; or (ii) a heavy chain variable region amino acid sequence derived from a human VH3-DP-47/V3-23 (VHIII) germline sequence and a light chain variable region amino acid sequence derived from a human L6 (VKI) germline sequence.

49. The method of claim 1, wherein said antibody is an antibody fragment

or a single-chain antibody.

50. The method of claim 1, wherein said antibody is conjugated to a cytotoxic agent, a radioisotope, or a drug.

51. The method of claim 1, wherein said antibody is a bispecific or multispecific molecule comprising a binding specificity for a human effector cell.

52. The method of claim 1, wherein said antibody is a bispecific or multispecific molecule comprising a binding specificity for CD3, CD4, CD138, IL-15R, membrane bound or receptor bound TNF-.gamma., a human Fc receptor, or membrane bound or receptor bound IL-15.

53. The method of claim 1, wherein said tumor cells are multiple myeloma cells or chronic lymhocytic leukemia cells.

54. The method of claim 1, wherein said tumor cells are recurrent or refractory tumor cells.

55. The method of claim 1, wherein said individual is 65 or more than 65 years old.

56. The method of any of claim 1, wherein said individual is less than 65 years old.

57. The method of claim 1, wherein said individual has not undergone previous anti-cancer treatment for the same cancer.

58. The method of claim 1, wherein said individual has not responded to a previous anti-cancer treatment for the same cancer.

59. The method of claim 1, wherein said individual has previously undergone autologous peripheral stem cell or bone marrow transplantation.

60. The method of claim 1, wherein said individual is enrolled to undergo subsequent autologous peripheral stem cell or bone marrow transplantation.

61. The method of claim 1, wherein the antibody, at least one corticosteroid and at least one non-corticosteroid chemotherapeutic agent are administered simultaneously.

62. The method of claim 1, wherein the antibody, at least one corticosteroid and at least one non-corticosteroid chemotherapeutic agent are administered sequentially.

63. The method of claim 1, wherein the antibody, at least one

corticosteroid and at least one non-corticosteroid chemotherapeutic agent are all administered separately.

64. The method of claim 1, wherein the antibody, at least one corticosteroid and at least one non-corticosteroid chemotherapeutic agent are co-administered in one or two pharmaceutical compositions.

65. The method of claim 62, wherein the antibody is administered at least 1 day, such as at least 2 days, e.g. at least one week, before administration of said at least one corticosteroid and said at least one non-corticosteroid chemotherapeutic agent.

66. The method of claim 1, wherein the antibody is administered in a dose of 1 mg/kg or more, such as a dose of from 1 to 20 mg/kg, e.g. a dose of from 5 to 20 mg/kg, e.g. a dose of 8 mg/kg.

67. The method of claim 1, wherein the antibody is administered once weekly for 2 to 12 weeks, such as for 3 to 10 weeks, such as for 4 to 8 weeks.

68. (canceled)

69. (canceled)

70. Use of an antibody that binds CD38 in the manufacture of a medicament for the treatment of cancer, wherein the medicament is for administration, or to be administered, in combination therapy with at least one corticosteroid and at least one non-corticosteroid chemotherapeutic agent.

71. (canceled)

72. A therapeutic combination for inhibiting growth and/or proliferation of tumor cells expressing CD38, comprising i) a non-agonistic antibody which binds to CD38, ii) at least one corticosteroid, and iii) at least one non-corticosteroid chemotherapeutic agent, wherein the combination is suitable for separate, sequential and/or simultaneous administration.

73. (canceled)

L25 ANSWER 8 OF 24 USPATFULL on STN

PI US 20100009934 A1 20100114

CLM What is claimed is:

1. (canceled)

2. (canceled)

3. (canceled)

4. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of a BAR agonist and

a second compound selected from a PDE inhibitor, an A2A receptor agonist, an antiproliferative compound, and an IL-6 agonist, in an amount effective to treat said B-cell proliferative disorder.

5. (canceled)

6. The method of claim 4, wherein said BAR agonist is selected from the group consisting of arbutaline, arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol, formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol, levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol, salmeterol, tulobuterol, terbutaline, and xamoterol.

7. The method of any of claim 4, wherein said BAR agonist is selected from Table 1 or 2.

8. The method of any of claim 4, wherein said B-cell proliferative disorder is selected from the group consisting of autoimmune lymphoproliferative disease, B-cell chronic lymphocytic leukemia (CLL), B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT type), nodal marginal zone lymphoma, splenic marginal zone lymphoma, hairy cell leukemia, plasmacytoma, diffuse large B-cell lymphoma, Burkitt lymphoma, multiple myeloma, indolent myeloma, smoldering myeloma, monoclonal gammopathy of unknown significance (MGUS), B-cell non-Hodgkin's lymphoma, small lymphocytic lymphoma, monoclonal immunoglobin deposition diseases, heavy chain diseases, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, precursor B-lymphoblastic leukemia/lymphoma, Hodgkin's lymphoma (e.g., nodular lymphocyte predominant Hodgkin's lymphoma, classical Hodgkin's lymphoma, nodular sclerosis Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, lymphocyte-rich classical Hodgkin's lymphoma, and lymphocyte depleted

Hodgkin's lymphoma), post-transplant lymphoproliferative disorder, and Waldenstrom's macroglobulinemia.

9. The method of claim 4, wherein said B-cell proliferative disorder is multiple myeloma.

10. The method of claim 4, wherein said second compound is said IL-6 agonist selected from the group consisting of IL-6, cytokines, soluble IL-6 receptor, platelet-derived growth factor, prostaglandin E1, forskolin, cholera toxin, dibutyryl cAMP, and IL-6 receptor agonists.

11. The method of claim 4, wherein, when said B-cell proliferative disorder is mantle cell lymphoma, said BAR agonist is not salmeterol administered with CHOP or bortezomib; when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salbutamol administered with VAD; when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salmeterol administered with prednisone and melphalan; when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salbutamol administered with clodronate; or when said B-cell proliferative disorder is multiple myeloma, said BAR agonist is not salbutamol administered with melphalan, prednisone, and pamidronate for multiple myeloma.

12. The method of claim 4, wherein said patient is not suffering from asthma, bronchiolitis obliterans, COPD, or shortness of breath.

13. The method of claim 4, wherein said patient is not suffering from an immunoinflammatory disorder of the lungs.

14. The method of claim 4, wherein said patient is not suffering from an immunoinflammatory disorder.

15. The method of claim 4, wherein said patient is not preparing to undergo, undergoing, or recovering from allogenic or autologous stem cell replacement.

16. The method of claim 4, wherein said patient is not concomitantly treated with a stem cell mobilizer.

17. The method of claim 4, wherein said patient is not concomitantly treated with an mTOR inhibitor and capecitabine.

18. The method of claim 4, wherein said BAR agonist is not isoproterenol.

19. The method of claim 4, wherein said BAR agonist is formulated for oral or intravenous administration.

20. The method of claim 4, wherein said BAR agonist and said A2A agonist, PDE inhibitor, antiproliferative compound, or IL-6 agonist are administered simultaneously.

21. The method of claim 4, wherein said BAR agonist and said A2A agonist, PDE inhibitor, antiproliferative compound, or IL-6 agonist are administered within 14 days of one another.

22. The method of claim 4, wherein said second compound is said A2A agonist selected from Table 3 or 4, or said second compound is said PDE inhibitor selected from Table 5 or 6.

23. The method of claim 4, wherein said second compound is said antiproliferative compound selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors,

ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D inhibitors, NF-kB inhibitors and pathway modulators, anthracyclines, histone deacetylase inhibitors, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, AKT inhibitors, PI3K inhibitors, TRAF inhibitors, statins, mitotic kinase inhibitors, KSP inhibitors, cyclin dependent kinase inhibitors, inhibitors of anti-apoptotic proteins, immune therapies, calcineurin antagonists, and IMiDs.

24. The method of claim 4, wherein said second compound is said antiproliferative compound selected from Table 7 or 8.

25. The method of claim 4, wherein said second compound is said antiproliferative compound and the combination of BAR agonist and antiproliferative compound is selected from Table 9.

26. The method of claim 4, wherein said BAR agonist is a beta 2 agonist.

27. (canceled)

28. (canceled)

29. (canceled)

30. (canceled)

31. (canceled)

32. A pharmaceutical composition comprising a BAR agonist and a second compound selected from the group consisting of an A2A agonist, a PDE inhibitor, an antiproliferative compound, and an IL-6 agonist, in an amount effective to treat a B-cell proliferative disorder.

33. The composition of claim 32, wherein said second compound is said A2A agonist selected from Table 3 or 4, or said second compound is said PDE inhibitor selected from Table 5 or 6.

34. The composition of claim 32, wherein said second compound is said antiproliferative compound selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase

inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D inhibitors, NF-kB inhibitors and pathway modulators, anthracyclines, histone deacetylase inhibitors, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, AKT inhibitors, PI3K inhibitors, TRAF inhibitors, statins, mitotic kinase inhibitors, KSP inhibitors, cyclin dependent kinase inhibitors, inhibitors of anti-apoptotic proteins, immune therapies, calcineurin antagonists, and IMiDs.

35. The composition of claim 32, wherein said second compound is said antiproliferative compound selected from Table 7 or 8.

36. The composition of claim 32, wherein said second compound is said antiproliferative compound and the combination of BAR agonist and

antiproliferative compound is selected from Table 9.

37-48. (canceled)

49. The composition of claim 32, wherein said BAR agonist is arbutaline,

arfomoterol, bambuterol, bitolterol, broxaterol, clenbuterol, fenoterol,

formoterol, hexoprenaline, indacaterol, isoetharine, isoproterenol,

levalbuterol, meluadrine, metaproterenol, nylidrin, picumeterol,

pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salbutamol,

salmeterol, tulobuterol, terbutaline, and xamoterol.

50. The composition of claim 32, wherein said BAR agonist is selected from Table 1 or 2.

51. The composition of claim 32, wherein said second compound is said IL-6 agonist selected from the group consisting of IL-6, cytokines,

soluble IL-6 receptor, platelet-derived growth factor, prostaglandin E1,

forskolin, cholera toxin, dibutyryl cAMP, and IL-6 receptor agonists.

L25 ANSWER 9 OF 24 USPATFULL on STN

PI US 20090252710 A1 20091008

CLM What is claimed is:

1. A method of suppressing the proliferation of tumor cells comprising contacting the tumor cells with human placental perfusate cells.

2. The method of claim 1, wherein the tumor cells are blood cancer cells.

3. The method of claim 1, wherein the tumor cells are solid tumor cells.

4. The method of claim 1, wherein the tumor cells are primary ductal carcinoma cells, leukemia cells, acute T cell leukemia cells, chronic myeloid lymphoma (CML) cells, acute myelogenous leukemia cells, chronic myelogenous leukemia (CML) cells, lung carcinoma cells, colon adenocarcinoma cells, histiocytic lymphoma cells, colorectal carcinoma cells, colorectal adenocarcinoma cells, or retinoblastoma cells.

5. The method of claim 1, wherein said perfusate comprises a culture medium.

6. The method of claim 1, wherein said perfusate has been treated to remove a plurality of erythrocytes.

7. The method of claim 1, wherein said contacting is contacting in vitro.

8. The method of claim 1, wherein said contacting is contacting in vivo.

9. The method of claim 8, wherein said contacting is in a human.

10. The method of claim 1, wherein said plurality of placental perfusate cells are total nucleated cells from placental perfusate.

11. The method of claim 1, wherein said placental perfusate cells comprise at least about 50% CD56.sup.+ placental cells.

12. A method of suppressing the proliferation of tumor cells comprising contacting the tumor cells with a plurality of CD56.sup.+, CD16.sup.- placental intermediate natural killer (PINK) cells.

13. The method of claim 12, wherein said contacting takes place in vitro.

14. The method of claim 12, wherein said contacting takes place in

vivo.

15. The method of claim 14, wherein said contacting takes place in a human.

16. The method of claim 12, wherein said tumor cells are primary ductal carcinoma cells, leukemia cells, acute T cell leukemia cells, chronic myeloid lymphoma (CML) cells, acute myelogenous leukemia cells, chronic myelogenous leukemia (CML) cells, lung carcinoma cells, colon adenocarcinoma cells, histiocytic lymphoma cells, multiple myeloma cells, colorectal carcinoma cells, colorectal adenocarcinoma cells, or retinoblastoma cells.

17. The method of claim 12, wherein said PINK cells are contacted with an immunomodulatory compound in an amount and for a time sufficient for said PINK cells to express detectably more granzyme B than an equivalent number of PINK cells not contacted with said immunomodulatory compound.

18. The method of claim 17, wherein said immunomodulatory compound is lenalidomide or pomalidomide.

19. A method of suppressing the proliferation of tumor cells comprising

contacting the tumor cells with combined natural killer cells, wherein said combined natural killer cells comprise natural killer cells isolated from placental perfusate and natural killer cells isolated from umbilical cord blood, and wherein said umbilical cord blood is isolated from the placenta from which said placental perfusate is obtained.

20. The method of claim 19, wherein said contacting takes place in vitro.

21. The method of claim 19, wherein said contacting takes place in vivo.

22. The method of claim 21, wherein said contacting takes place in a human.

23. The method of claim 19, wherein said tumor cells are primary ductal carcinoma cells, leukemia cells, acute T cell leukemia cells, chronic myeloid lymphoma (CML) cells, acute myelogenous leukemia cells, chronic myelogenous leukemia (CML) cells, lung carcinoma cells, colon adenocarcinoma cells, histiocytic lymphoma cells, multiple myeloma cells, colorectal carcinoma cells, colorectal adenocarcinoma cells, or retinoblastoma cells.

24. The method of claim 19, wherein said combined natural killer cells comprise: a detectably higher number of CD3.sup.-CD56.sup.+CD16.sup.- natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably lower number of CD3.sup.-CD56.sup.+CD16.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+KIR2DL2/L3.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably lower number of CD3 CD56.sup.+NKp46.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+NKp30.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+2B4.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; or a detectably higher number of CD3.sup.-CD56.sup.+CD94.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood.

25. The method of claim 24, wherein said natural killer cells have not

been cultured.

26. The method of claim 19, wherein said combined natural killer cells comprise: a detectably lower number of CD3.sup.-CD56.sup.+ KIR2DL2/L3.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+NKp46.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+ NKp44.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood; a detectably higher number of CD3.sup.-CD56.sup.+NKp30.sup.+ natural killer cells than an equivalent number of natural killer cells from peripheral blood.

27. The method of claim 26, wherein said natural killer cells have been cultured.

28. The method of claim 27, wherein said natural killer cells have been cultured for about 21 days.

L25 ANSWER 10 OF 24 USPATFULL on STN

PI US 20090232796 A1 20090917

CLM What is claimed is:

1. A method of treating cancer in a patient, comprising administering to

the patient (i) an effective amount of CD40L, derivative, or fragment thereof, and (ii) an effective amount of an immunomodulatory compound, wherein the immunomodulatory compound is a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof: ##STR46## wherein: one of X and Y is C.dbd.O, the other of X and Y is C.dbd.O or CH.sub.2; R.sup.2 is hydrogen or lower alkyl; ##STR47## wherein: one of X and Y is C.dbd.O and the other of X and Y is

C.dbd.O or CH.sub.2; (i) each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4,

independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, or (ii) one of R.sup.1, R.sup.2, R.sup.3,

and R.sup.4 is --NHR.sup.5 and the remaining of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are hydrogen; R.sup.5 is hydrogen or alkyl of 1 to 8 carbon atoms; R.sup.6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzyl, or halo; provided that R.sup.6 is other than hydrogen if X and Y

are C.dbd.O and (i) each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is fluoro or (ii) one of R.sup.1, R.sup.2, R.sup.3, or R.sup.4 is amino; ##STR48## wherein: one of X and Y is C.dbd.O and the other is CH.sub.2

or C.dbd.O; R.sup.1 is H, (C.sub.1-C.sub.8)alkyl,

(C.sub.3-C.sub.7)cycloalkyl, (C.sub.2-C.sub.8)alkenyl,

(C.sub.2-C.sub.8)alkynyl, benzyl, aryl, (C.sub.0-C.sub.4)alkyl

C.sub.1-C.sub.6)heterocycloalkyl, (C.sub.0-C.sub.4)alkyl

C.sub.2-C.sub.5)heteroaryl, C(O)R.sup.3, C(S)R.sup.3, C(O)OR.sup.4,

(C.sub.1-C.sub.8)alkyl-N(R.sup.6).sub.2,

(C.sub.1-C.sub.8)alkyl-OR.sup.5, (C.sub.1-C.sub.8)alkyl-C(O)OR.sup.5,

C(O)NHR.sup.3, C(S)NHR.sup.3, C(O)NR.sup.3R.sup.3, C(S)NR.sup.3R.sup.3

or (C.sub.1-C.sub.8)alkyl-O(CO)R.sup.5; R.sup.2 is H, F, benzyl,

(C.sub.1-C.sub.8)alkyl, (C.sub.2-C.sub.8)alkenyl, or

(C.sub.2-C.sub.8)alkynyl; R.sup.3 and R.sup.3' are independently

(C.sub.1-C.sub.8)alkyl, (C.sub.3-C.sub.7)cycloalkyl,

(C.sub.2-C.sub.8)alkenyl, (C.sub.2-C.sub.8)alkynyl, benzyl, aryl,

(C.sub.0-C.sub.4)alkyl-(C.sub.1-C.sub.6)heterocycloalkyl,

(C.sub.0-C.sub.4)alkyl-(C.sub.2-C.sub.5)heteroaryl,

(C.sub.0-C.sub.8)alkyl-N(R.sup.6).sub.2,

(C.sub.1-C.sub.8)alkyl-OR.sup.5, (C.sub.1-C.sub.8)alkyl-C(O)OR.sup.5,

(C.sub.1-C.sub.8)alkyl-O(CO)R.sup.5, or C(O)OR.sup.5; R.sup.4 is

(C.sub.1-C.sub.8)alkyl, (C.sub.2-C.sub.8)alkenyl,

(C.sub.2-C.sub.8)alkynyl, (C.sub.1-C.sub.4)alkyl-OR.sup.5, benzyl,
aryl,

(C.sub.0-C.sub.4)alkyl-C.sub.1-C.sub.6)heterocycloalkyl, or

(C.sub.0-C.sub.4)alkyl-(C.sub.2-C.sub.5)heteroaryl; R.sup.5 is

(C.sub.1-C.sub.8)alkyl, (C.sub.2-C.sub.8)alkenyl,

(C.sub.2-C.sub.8)alkynyl, benzyl, aryl, or (C.sub.2-C.sub.5)heteroaryl;

R.sup.6 is independently H, (C.sub.1-C.sub.8)alkyl,

(C.sub.2-C.sub.8)alkenyl, (C.sub.2-C.sub.8)alkynyl, benzyl, aryl,

(C.sub.2-C.sub.5)heteroaryl, or (C.sub.0-C.sub.8)alkyl-C(O)O--R.sup.5 or

the R.sup.6 groups can join to form a heterocycloalkyl group; n is 0 or 1; and * is a chiral-carbon center; ##STR49## wherein: one of X and Y is C.dbd.O and the other is CH.sub.2 or C.dbd.O; R is H or CH.sub.2OCOR'; (i) each of R.sup.1, R.sup.2, R.sup.3, or R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2, R.sup.3, or R.sup.4 is nitro or --NHR.sup.5 and the remaining of R.sup.1, R.sup.2, R.sup.3, or R.sup.4 are hydrogen; R.sup.5 is hydrogen or alkyl of 1 to 8 carbons R.sup.6 hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro; R' is R.sup.7--CHR.sup.10--N(R.sup.8R.sup.9); R.sup.7 is m-phenylene or p-phenylene or --(C.sub.nH.sub.2n)-- in which n has a value of 0 to 4; each of R.sup.8 and R.sup.9 taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R.sup.8 and R.sup.9 taken together are tetramethylene, pentamethylene, hexamethylene, or --CH.sub.2CH.sub.2X.sub.1CH.sub.2CH.sub.2-- in which X.sub.1 is --O--, --S--, or --NH--; R.sup.10 is hydrogen, alkyl of to 8

carbon atoms, or phenyl; and * represents a chiral-carbon center;

##STR50## wherein: one of X and Y is C.dbd.O and the other of X and Y is

C.dbd.O or CH.sub.2; (i) each of R.sup.1, R.sup.2, R.sup.3, or R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is --NHR.sup.5 and the remaining of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are hydrogen; R.sup.5 is hydrogen or alkyl of 1 to 8 carbon atoms; R.sup.6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro; R.sup.7 is m-phenylene or p-phenylene or --(C.sub.nH.sub.2n)-- in which n has a value of 0 to 4; each of R.sup.8 and R.sup.9 taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R.sup.8 and R.sup.9 taken together are tetramethylene, pentamethylene, hexamethylene, or --CH.sub.2CH.sub.2X.sup.1CH.sub.2CH.sub.2-- in which X.sup.1 is --O--, --S--, or --NH--; and R.sup.10 is hydrogen, alkyl of to 8 carbon atoms, or phenyl; ##STR51## wherein: one of X and Y is C.dbd.O and the other of X and Y is C.dbd.O or CH.sub.2; (i) each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is nitro or protected amino and the remaining of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are hydrogen; and R.sup.6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro,

or

fluoro; ##STR52## wherein: one of X and Y is C.dbd.O and the other of X

and Y is C.dbd.O or CH.sub.2; (i) each of R.sup.1, R.sup.2, R.sup.3, and

R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon

atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2,

R.sup.3, and R.sup.4 is --NHR.sup.5 and the remaining of R.sup.1,

R.sup.2, R.sup.3, and R.sup.4 are hydrogen; R.sup.5 is hydrogen, alkyl

of 1 to 8 carbon atoms, or CO--R.sup.7--CH(R.sup.10)NR.sup.8R.sup.9 in

which each of R.sup.7, R.sup.8, R.sup.9, and R.sup.10 is as herein

defined; and R.sup.6 is alkyl of 1 to 8 carbon atoms, benzo, chloro, or

fluoro; ##STR53## wherein: one of X and Y is C.dbd.O and the other of X

and Y is C.dbd.O or CH.sub.2; R.sup.6 is hydrogen, alkyl of 1 to 8

carbon atoms, benzyl, chloro, or fluoro; R.sup.7 is m-phenylene,

p-phenylene or --(C.sub.nH.sub.2n)-- in which n has a value of 0 to 4;

each of R.sup.8 and R.sup.9 taken independently of the other is hydrogen

or alkyl of 1 to 8 carbon atoms, or R.sup.8 and R.sup.9 taken together

are tetramethylene, pentamethylene, hexamethylene, or

--CH.sub.2CH.sub.2X.sup.1CH.sub.2CH.sub.2-- in which X.sup.1 is --O--,

--S-- or --NH--; and R.sup.10 is hydrogen, alkyl of 1 to 8 carbon atoms,

or phenyl; ##STR54## wherein: Y is oxygen or H.sup.2 and each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4, independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or amino; ##STR55## wherein: each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms; ##STR56## wherein: Y is

Oxygen or H.sub.2, a first of R.sup.1 and R.sup.2 is halo, alkyl, alkoxy, alkylamino, dialkylamino, cyano, or carbamoyl, the second of R.sup.1 and R.sup.2, independently of the first, is hydrogen, halo, alkyl, alkoxy, alkylamino, dialkylamino, cyano, or carbamoyl, and R.sup.3 is hydrogen, alkyl, or benzyl; ##STR57## wherein: a first of R.sup.1 and R.sup.2 is halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of from

1 to 4 carbon atoms, cyano, or carbamoyl; the second of R.sup.1 and R.sup.2, independently of the first, is hydrogen, halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, alkylamino in which alkyl is of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of from 1 to 4 carbon atoms, cyano, or carbamoyl; and R.sup.3 is hydrogen, alkyl of from 1 to 4 carbon atoms, or benzyl; ##STR58## wherein: when n is not zero and R.sup.1 is not the same as R.sup.2, C* is a center of chirality; one of X.sup.1 and X.sup.2 is amino, nitro,

alkyl of one to six carbons, or NH-Z, and the other of X.sup.1 or X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2 independent of the other, is hydroxy or NH-Z; R.sup.3 is hydrogen, alkyl of one to six carbons, halo, or haloalkyl; Z is hydrogen, aryl, alkyl of one to six carbons, formyl, or acyl of one to six carbons; and n has a value of 0, 1, or 2; provided that if X.sup.1 is amino, and n is 1 or 2, then R.sup.1 and R.sup.2 are not both hydroxy; ##STR59## wherein: when n is not zero and R.sup.1 is not R.sup.2, C* is a center of chirality; one of X and X.sup.2 is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of X or X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2 independent of the other, is hydroxy or NH-Z; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, aryl or an alkyl or acyl of one to six carbons; and n has a value of 0, 1, or 2; ##STR60## wherein: when n is not zero and R.sup.1 is not R.sup.2, C* is a center of chirality; one of X.sup.1 and X.sup.2 is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of X.sup.1 or X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2 independent of the other, is hydroxy or NH-Z; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, aryl, or an alkyl or acyl of one to six carbons; and n has a value of 0, 1, or 2; ##STR61## wherein: one of X.sup.1 and X.sup.2 is nitro, or NH-Z, and the other of X.sup.1 or

X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2, independent of the other, is hydroxy or NH-7; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, phenyl, an acyl of one to six carbons, or an alkyl of one to six carbons; n has a value of 0, 1, or 2; and if --COR.sup.2 and --(CH.sub.2).sub.nCOR.sup.1 are different, C* is a center of chirality; ##STR62## wherein: one of X.sup.1 and X.sup.2 is alkyl of one to six carbons; each of R.sup.1 and R.sup.2, independent of the other, is hydroxy or NH-Z; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, phenyl, an acyl of one to six carbons, or an alkyl of one to six carbons; n has a value of 0, 1, or 2; and if --COR.sup.2 and --(CH.sub.2).sub.nCOR.sup.1 are different, C* is a center of chirality; ##STR63## wherein: the * carbons are centers of chirality; X is --C(O)-- or --CH.sub.2--; R.sup.1 is alkyl of 1 to 8 carbon atoms or --NHR.sup.3; R.sup.2 is hydrogen, alkyl of 1 to 8 carbon atoms, or halogen; and R.sup.3 is hydrogen, alkyl of 1 to 8 carbon atoms, unsubstituted or substituted with alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, phenyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino

of 1 to 4 carbon atoms, benzyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, or --COR.sup.4, wherein R.sup.4 is hydrogen, alkyl of 1 to 8 carbon atoms, unsubstituted or substituted with alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, phenyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, or benzyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms.

2. The method of claim 1, wherein the immunomodulatory compound is administered before, concurrently with, or after the administration of the CD40L, derivative, or fragment thereof.

3. The method of claim 2, wherein the immunomodulatory compound is administered from about 1, 6, 12, or 24 hours to about 2 days, 4 days, 1 week, or about 2 weeks before the administration of the CD40L, derivative, or fragment thereof.

4. The method of claim 1, wherein the cancer is solid or hematological cancer.

5. The method of claim 1, wherein the cancer is a leukemia, lymphoma or myeloma.

6. The method of claim 5, wherein the leukemia is chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), prolymphocytic leukemia (PLL), hairy cell leukemia, or small lymphocytic leukemia (SLL).

7. The method of claim 5, wherein the lymphoma is selected from the group consisting of Mantle cell lymphoma, splenic lymphoma, hodgkin's lymphoma, mucosal associated lymphoid tissue lymphoma, diffuse small lymphocytic lymphoma, follicular lymphoma, mocytoid B cell lymphoma, Burkitt's lymphoma, AIDS-related lymphoma, diffuse large B-cell lymphoma, lymphomatoid granulomatosis, intravascular lymphomatosis, intravascular lymphoma, cutaneous B-cell lymphoma, and non-hodgkins lymphoma.

8. The method of claim 1, wherein the cancer is multiple myeloma.

9. The method of claim 1, wherein the immunomodulatory compound is

1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline or

1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline.

10. The method of claim 1, wherein the immunomodulatory compound is administered in an amount between about 2 to about 100 mg/kg.

11. The method of claim 1, wherein the immunomodulatory compound is administered orally, parenterally, or topically.

12. The method of claim 1, further comprising administering an effective

amount of an anti-CD40 antibody or a fragment thereof.

13. A method of treating leukemia or lymphoma in a patient, comprising administering to the patient: (i) an effective amount of an anti-CD40 antibody or a fragment thereof, and (ii) an effective amount of an immunomodulatory compound, wherein the immunomodulatory compound is a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof: ##STR64## wherein: one of X and Y is C.dbd.O, the other of X and Y is C.dbd.O or CH.sub.2; R.sup.2 is hydrogen or lower alkyl; ##STR65## wherein: one of X and Y is C.dbd.O and the other of X and Y is C.dbd.O or CH.sub.2; (i) each of R.sup.1,

R.sup.2, R.sup.3, and R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, or (ii) one of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is --NHR.sup.5 and the remaining of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are hydrogen; R.sup.5 is hydrogen or alkyl of 1 to 8 carbon atoms; R.sup.6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzyl, or halo; provided that R.sup.6 is other than hydrogen if X and Y are C.dbd.O and (i) each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is fluoro or (ii) one of R.sup.1, R.sup.2, R.sup.3, or R.sup.4 is amino; ##STR66## wherein: one of X and Y is C.dbd.O and the other is CH.sub.2 or C.dbd.O; R.sup.1 is H, (C.sub.1-C.sub.8)alkyl, (C.sub.3-C.sub.7)cycloalkyl, (C.sub.2-C.sub.8)alkenyl, (C.sub.2-C.sub.8)alkynyl, benzyl, aryl, (C.sub.0-C.sub.4)alkyl C.sub.1-C.sub.6)heterocycloalkyl, (C.sub.0-C.sub.4)alkyl C.sub.2-C.sub.5)heteroaryl, C(O)R.sup.3, C(S)R.sup.3, C(O)OR.sup.4, (C.sub.1-C.sub.8)alkyl-N(R.sup.6).sub.2, (C.sub.1-C.sub.8)alkyl-OR.sup.5, (C.sub.1-C.sub.8)alkyl-C(O)OR.sup.5, C(O)NHR.sup.3, C(S)NHR.sup.3, C(O)NR.sup.3R.sup.3, C(S)NR.sup.3R.sup.3 or (C.sub.1-C.sub.8)alkyl-O(CO)R.sup.5; R.sup.2 is H, F, benzyl, (C.sub.1-C.sub.8)alkyl, (C.sub.2-C.sub.8)alkenyl, or (C.sub.2-C.sub.8)alkynyl; R.sup.3 and R.sup.3' are independently (C.sub.1-C.sub.8)alkyl, (C.sub.3-C.sub.7)cycloalkyl, (C.sub.2-C.sub.8)alkenyl, (C.sub.2-C.sub.8)alkynyl, benzyl, aryl,

(C.sub.0-C.sub.4)alkyl-(C.sub.1-C.sub.6)heterocycloalkyl,

(C.sub.0-C.sub.4)alkyl-(C.sub.2-C.sub.5)heteroaryl,

(C.sub.0-C.sub.8)alkyl-N(R.sup.6).sub.2,

(C.sub.1-C.sub.8)alkyl-OR.sup.5, (C.sub.1-C.sub.8)alkyl-C(O)OR.sup.5,

(C.sub.1-C.sub.8)alkyl-O(CO)R.sup.5, or C(O)OR.sup.5; R.sup.4 is

(C.sub.1-C.sub.8)alkyl, (C.sub.2-C.sub.8)alkenyl,

(C.sub.2-C.sub.8)alkynyl, (C.sub.1-C.sub.4)alkyl-OR.sup.5, benzyl,
aryl,

(C.sub.0-C.sub.4)alkyl(C.sub.1-C.sub.6)heterocycloalkyl, or

(C.sub.0-C.sub.4)alkyl-(C.sub.2-C.sub.5)heteroaryl; R.sup.5 is

(C.sub.1-C.sub.8)alkyl, (C.sub.2-C.sub.8)alkenyl,

(C.sub.2-C.sub.8)alkynyl, benzyl, aryl, or (C.sub.2-C.sub.5)heteroaryl;
R.sup.6 is independently H, (C.sub.1-C.sub.8)alkyl,

(C.sub.2-C.sub.8)alkenyl, (C.sub.2-C.sub.8)alkynyl, benzyl, aryl,

(C.sub.2-C.sub.5)heteroaryl, or (C.sub.0-C.sub.8)alkyl-C(O)O--R.sup.5
or

the R.sup.6 groups can join to form a heterocycloalkyl group; n is 0 or
1; and * is a chiral-carbon center; ##STR67## wherein: one of X and Y
is C.dbd.O and the other is CH.sub.2 or C.dbd.O; R is H or
CH.sub.2OCOR'; (i) each of R.sup.1, R.sup.2, R.sup.3, or R.sup.4,
independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or
alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2, R.sup.3,
or R.sup.4 is nitro or --NHR.sup.5 and the remaining of R.sup.1,

R.sup.2, R.sup.3, or R.sup.4 are hydrogen; R.sup.5 is hydrogen or alkyl of 1 to 8 carbons R.sup.6 hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro; R' is R.sup.7--CHR.sup.10--N(R.sup.8R.sup.9); R.sup.7 is m-phenylene or p-phenylene or --(C.sub.nH.sub.2n)-- in which n has a value of 0 to 4; each of R.sup.8 and R.sup.9 taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R.sup.8 and R.sup.9 taken together are tetramethylene, pentamethylene, hexamethylene, or --CH.sub.2CH.sub.2X.sub.1CH.sub.2CH.sub.2-- in which X.sup.1 is --O--, --S--, or --NH--; R.sup.10 is hydrogen, alkyl of to 8 carbon atoms, or phenyl; and * represents a chiral-carbon center;

##STR68## wherein: one of X and Y is C.dbd.O and the other of X and Y is C.dbd.O or CH.sub.2; (i) each of R.sup.1, R.sup.2, R.sup.3, or R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is --NHR.sup.5 and the remaining of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are hydrogen; R.sup.5 is hydrogen or alkyl of 1 to 8 carbon atoms; R.sup.6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro; R.sup.7 is m-phenylene or p-phenylene or --(C.sup.nH.sub.2n)-- in which n has a value of 0 to 4; each of R.sup.8 and R.sup.9 taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R.sup.8 and R.sup.9 taken together are

tetramethylene, pentamethylene, hexamethylene, or --CH.sub.2CH.sub.2X.sup.1CH.sub.2CH.sub.2-- in which X.sup.1 is --O--, --S--, or --NH--; and R.sup.10 is hydrogen, alkyl of to 8 carbon atoms, or phenyl; ##STR69## wherein: one of X and Y is C.dbd.O and the other of X and Y is C.dbd.O or CH.sub.2; (i) each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is nitro or protected amino and the remaining of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are hydrogen; and R.sup.6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro; ##STR70## wherein: one of X and Y is C.dbd.O and the other of X and Y is C.dbd.O or CH.sub.2; (i) each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 is --NHR.sup.5 and the remaining of R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are hydrogen; R.sup.5 is hydrogen, alkyl of 1 to 8 carbon atoms, or CO--R.sup.7--CH(R.sup.10)NR.sup.8R.sup.9 in which each of R.sup.7, R.sup.8, R.sup.9, and R.sup.10 is as herein defined; and R.sup.6 is alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro; ##STR71## wherein: one of X and Y is C.dbd.O and the other of X

and Y is C.dbd.O or CH.sub.2; R.sup.6 is hydrogen, alkyl of 1 to 8 carbon atoms, benzyl, chloro, or fluoro; R.sup.7 is m-phenylene, p-phenylene or --(C.sup.nH.sub.2n)-- in which n has a value of 0 to 4; each of R.sup.8 and R.sup.9 taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R.sup.8 and R.sup.9 taken together are tetramethylene, pentamethylene, hexamethylene, or --CH.sub.2CH.sub.2X.sup.1CH.sub.2CH.sub.2-- in which X.sup.1 is --O--, --S-- or --NH--; and R.sup.10 is hydrogen, alkyl of 1 to 8 carbon atoms, or phenyl; ##STR72## wherein: Y is oxygen or H.sup.2 and each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4, independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or amino; ##STR73## wherein: each of R.sup.1, R.sup.2, R.sup.3, and R.sup.4, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms; ##STR74## wherein: Y is Oxygen or H.sub.2, a first of R.sup.1 and R.sup.2 is halo, alkyl, alkoxy, alkylamino, dialkylamino, cyano, or carbamoyl, the second of R.sup.1 and R.sup.2, independently of the first, is hydrogen, halo, alkyl, alkoxy, alkylamino, dialkylamino, cyano, or carbamoyl, and R.sup.3 is hydrogen, alkyl, or benzyl; ##STR75## wherein: a first of R.sup.1 and R.sup.2 is halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of

from

1 to 4 carbon atoms, cyano, or carbamoyl; the second of R.sup.1 and R.sup.2, independently of the first, is hydrogen, halo, alkyl of from 1 to 4 carbon atoms, alkoxy of from 1 to 4 carbon atoms, alkylamino in which alkyl is of from 1 to 4 carbon atoms, dialkylamino in which each alkyl is of from 1 to 4 carbon atoms, cyano, or carbamoyl; and R.sup.3 is hydrogen, alkyl of from 1 to 4 carbon atoms, or benzyl; ##STR76## wherein: when n is not zero and R.sup.1 is not the same as R.sup.2, C* is a center of chirality; one of X.sup.1 and X.sup.2 is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of X.sup.1 or X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2 independent of the other, is hydroxy or NH-Z; R.sup.3 is hydrogen, alkyl of one to six carbons, halo, or haloalkyl; Z is hydrogen, aryl, alkyl of one to six carbons, formyl, or acyl of one to six carbons; and n has a value of 0, 1, or 2; provided that if X.sup.1 is amino, and n is 1 or 2, then R.sup.1 and R.sup.2 are not both hydroxy; ##STR77## wherein: when n is not zero and R.sup.1 is not R.sup.2, C* is a center of chirality; one of

X.sup.1 and X.sup.2 is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of X.sup.1 or X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2 independent of the other, is hydroxy or NH-Z; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, aryl or an alkyl or acyl of one to six carbons; and n has a value of 0, 1, or

2;

##STR78## wherein: when n is not zero and R.sup.1 is not R.sup.2, C* is a center of chirality; one of X.sup.1 and X.sup.2 is amino, nitro, alkyl of one to six carbons, or NH-Z, and the other of X.sup.1 or X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2 independent of the other, is hydroxy or NH-Z; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, aryl, or an alkyl or acyl of one to six carbons; and n has a value of 0, 1, or 2; ##STR79## wherein: one of X.sup.1 and X.sup.2 is nitro, or NH-Z, and the other of X.sup.1 or X.sup.2 is hydrogen; each of R.sup.1 and R.sup.2, independent of the other, is hydroxy or NH-Z; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, phenyl, an acyl of one to six carbons, or an alkyl of one to six carbons; n has a value of 0, 1, or 2; and if --COR.sup.2 and --(CH.sub.2).sub.nCOR.sup.1 are different, C* is a center of chirality; ##STR80## wherein: one of X.sup.1 and X.sup.2 is alkyl of one to six carbons; each of R.sup.1 and R.sup.2, independent of the other, is hydroxy or NH-Z; R.sup.3 is alkyl of one to six carbons, halo, or hydrogen; Z is hydrogen, phenyl, an acyl of one to six carbons, or an alkyl of one to six carbons; n has a value of 0, 1, or 2; and if --COR.sup.2 and --(CH.sub.2).sub.nCOR.sup.1 are different, C* is a

center of chirality; ##STR81## wherein: the carbons are centers of chirality; X is --C(O)-- or --CH.sub.2--; R.sup.1 is alkyl of 1 to 8 carbon atoms or --NHR.sup.3; R.sup.2 is hydrogen, alkyl of 1 to 8 carbon atoms, or halogen; and R.sup.3 is hydrogen, alkyl of 1 to 8 carbon atoms, unsubstituted or substituted with alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, phenyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, benzyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, or --COR.sup.4, wherein R.sup.4 is hydrogen, alkyl of 1 to 8 carbon atoms, unsubstituted or substituted with alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, cycloalkyl of 3 to 18 carbon atoms, phenyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms, or benzyl, unsubstituted or substituted with alkyl of 1 to 8 carbon atoms, alkoxy of 1 to 8 carbon atoms, halo, amino, or alkylamino of 1 to 4 carbon atoms.

14. The method of claim 13, wherein the immunomodulatory compound is

administered before, concurrently with, or after administration of the anti-CD40 antibody or fragment thereof.

15. The method of claim 14, wherein the immunomodulatory compound is administered from about 1, 6, 12, or 24 hours to about 2 days, 4 days, 1 week, or about 2 weeks before administration of the anti-CD40 antibody or fragment thereof.

16. The method of claim 13, wherein the leukemia is chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), prolymphocytic leukemia (PLL), hairy cell leukemia, or small lymphocytic leukemia (SLL).

17. The method of claim 13, wherein the lymphoma is selected from the group consisting of Mantle cell lymphoma, splenic lymphoma, hodgkin's lymphoma, mucosal associated lymphoid tissue lymphoma, diffuse small lymphocytic lymphoma, follicular lymphoma, mocytoid B cell lymphoma, Burkitt's lymphoma, AIDS-related lymphoma, diffuse large B-cell lymphoma, lymphomatoid granulomatosis, intravascular lymphomatosis, intravascular lymphoma, cutaneous B-cell lymphoma, and non-hodgkins lymphoma.

18. The method of claim 13, wherein said immunomodulatory compound is 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline or 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline.

19. The method of claim 13, wherein said immunomodulatory compound is administered in an amount of between about 2 to about 100 mg/kg.

20. The method of claim 13, wherein said immunomodulatory compound is administered orally, parenterally, or topically.

L25 ANSWER 11 OF 24 USPATFULL on STN

PI US 20090155265 A1 20090618

CLM What is claimed is:

1-21. (canceled)

22. A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma a therapeutically effective amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the formula: ##STR9## or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, and administering a therapeutically effective amount of an antibody.

23. The method of claim 22, wherein the compound is ##STR10##

24. The method of claim 22, wherein the compound is a pharmaceutically acceptable salt.

25. The method of claim 22, wherein the compound is a pharmaceutically acceptable solvate.

26. The method of claim 22, wherein the compound is a pharmaceutically acceptable stereoisomer.

27. The method of claim 26, wherein the stereoisomer is an enantiomerically pure R isomer.

28. The method of claim 26, wherein the stereoisomer is an enantiomerically pure S isomer.

29. The method of claim 22, wherein the antibody is a monoclonal or polyclonal antibody.

30. The method of claim 29, wherein the antibody is a monoclonal antibody.

31. The method of claim 29, wherein the antibody is trastuzumab, rituximab, bevacizumab, pertuzumab, tositumomab, infliximab, edrecolomab or G250, or a combination thereof.

32. The method of claim 29, wherein the antibody is an anti-TNF-a antibody.

33. The method of claim 22, wherein the compound is administered concurrently, prior to, or following administration of the antibody.

34. The method of claim 22, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

35. The method of claim 22, wherein the multiple myeloma is relapsed, refractory or resistant to conventional therapy.

36. The method of claim 22, further comprising administering a therapeutically effective amount of dexamethasone, melphalan or prednisone.

37. The method of claim 22, wherein the compound is administered

orally.

38. The method of claim 37, wherein the compound is administered in the form of a capsule or tablet.

39. The method of claim 22, wherein the compound is administered in an amount of about 5, 10, 20, 25, 30 and 50 mg per day.

40. The method of claim 22, wherein the compound is administered in an amount of about 25 mg per day.

41. The method of claim 22, wherein the compound is administered cyclically.

42. The method of claim 41, wherein one cycle comprises four to six weeks.

43. The method of claim 41, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

44. The method of claim 43, wherein the compound is orally administered in an amount of from about 5 to about 25 mg per day for 21 days every 28

days.

45. The method of claim 44, wherein dexamethasone is orally administered

in an amount of 40 mg daily on days 1, 8, 15 and 22 every 28 days.

46. The method of claim 41, wherein the compound is orally administered

in an amount of about 25 mg per day for 21 days followed by seven days

rest in a 28 day cycle.

47. The method of claim 22, wherein the antibody is administered

intravenously or subcutaneously once or twice daily in an amount of from

about 1 to about 1000 mg.

48. The method of claim 47, wherein the antibody is administered

intravenously or subcutaneously once or twice daily in an amount of from

about 5 to about 500 mg.

49. The method of claim 48, wherein the antibody is administered

intravenously or subcutaneously once or twice daily in an amount of from

about 10 to about 350 mg.

50. The method of claim 49, wherein the antibody is administered intravenously or subcutaneously once or twice daily in an amount of from about 50 to about 200 mg.

51. The method of claim 36, wherein the capsule comprises the compound, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

52. A pharmaceutical composition suitable for treating multiple myeloma in a patient having multiple myeloma, comprising a therapeutically effective amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione of the formula: ##STR11## and a therapeutically effective amount of a monoclonal antibody.

L25 ANSWER 12 OF 24 USPATFULL on STN

PI US 20090068210 A1 20090312

CLM What is claimed is:

1. A method of providing an iNKT cell responsive to multiple myeloma

comprising: (i) isolating an iNKT cell from a patient having multiple myeloma; and (ii) incubating the isolated iNKT cell with an immunomodulatory compound.

2. The method of claim 1, further comprising contacting said iNKT cell with an multiple myeloma cell loaded with .alpha.-GalCer prior to step (ii).

3. The method of claim 1, wherein the iNKT cell is TCRV.alpha.24.sup.+ and TCRV.beta.11.sup.+.

4. The method of claim 1 wherein the multiple myeloma cell is CD1d-expressing primary myeloma cell.

5. The method of claim 4, wherein the primary myeloma cell is a multiple myeloma cell transfected with CD1d.

6. The method of claim 1, wherein the immunomodulatory compound is 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline or 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4 aminoisoindoline.

7. An iNKT cell, which is prepared according to the method of claim 1.

8. A pharmaceutical composition comprising the iNKT cell of claim 7.

9. A method of treating multiple myeloma in a patient comprising administering to said patient a therapeutically effective amount of the iNKT cell of claim 7.

10. A method of preparing a vaccine for multiple myeloma comprising: (i) isolating an iNKT cell from a patient having multiple myeloma; (ii) incubating said isolated iNKT cell with an immunomodulatory compound; and (iii) irradiating the iNKT cell from step (ii).

11. The method of claim 10, further comprising contacting said iNKT cell with a multiple myeloma cell loaded with .alpha.-GalCer prior to step (ii).

12. A method of preventing multiple myeloma in a human comprising administering to a human the vaccine prepared using the method of claim 10.

13. A method of treating or preventing multiple myeloma in a patient comprising: (i) isolating an iNKT cell from a patient having multiple myeloma; (ii) irradiating the iNKT cell from step (i); (iii)

administering the iNKT cell to the patient; and (iv) administering an immunomodulatory compound to the patient.

14. The method of claim 13, further comprising contacting said iNKT cell

with a multiple myeloma cell loaded with .alpha.-GalCer prior to step (ii).

L25 ANSWER 13 OF 24 USPATFULL on STN

PI US 20090053168 A1 20090226

CLM What is claimed is:

1. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient an A2A receptor agonist in an amount effective to treat said B-cell proliferative disorder.

2. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of an A2A receptor agonist and an antiproliferative compound in amounts that together are effective to treat said B-cell proliferative disorder.

3. The method of claim 1 or 2, wherein said A2A receptor agonist is selected from the group consisting of the compounds listed in Tables 1

and 2.

4. The method of claim 2, wherein said A2A receptor agonist and antiproliferative compound are administered simultaneously.

5. The method of claim 2, wherein said A2A receptor agonist and antiproliferative compound are administered within 14 days of one another.

6. The method of claim 2, wherein said antiproliferative compound is IL-6.

7. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of a PDE inhibitor and an antiproliferative compound other than a glucocorticoid in amounts that together are effective to treat said B-cell proliferative disorder.

8. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of two or more PDE inhibitors having activity against at least two of PDE 2, 3, 4, and 7 and an antiproliferative compound in amounts that together are effective

to treat said B-cell proliferative disorder.

9. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of a PDE inhibitor having activity against at least two of PDE 2, 3, 4, and 7 and an antiproliferative compound in amounts that together are effective to treat said B-cell proliferative disorder.

10. The method of claim 7 or 9, wherein said PDE inhibitor is selected from the group consisting of the compounds listed in Tables 5 and 6.

11. The method of claim 8, wherein at least one of said PDE inhibitors is selected from the group consisting of the compounds listed in Tables 5 and 6.

12. The method of claim 7, wherein said PDE inhibitor is active against at least two of PDE 2, 3,4, and 7.

13. The method of claim 7, wherein said combination comprises two or more PDE inhibitors that when combined are active against at least two of PDE 2, 3, 4, and 7.

14. The method of claim 7 or 9, wherein said PDE inhibitor and

antiproliferative compound are administered simultaneously.

15. The method of claim 7 or 9, wherein said PDE inhibitor and antiproliferative compound are administered within 14 days of one another.

16. The method of claim 8, wherein said PDE inhibitors and antiproliferative compound are administered simultaneously.

17. The method of claim 8, wherein said PDE inhibitors and antiproliferative compound are administered within 14 days of one another.

18. The method of claim 7, wherein said PDE inhibitor is active against PDE 4.

19. The method of claim 1, 2, 7, 8, or 9, wherein said B-cell proliferative disorder is selected from the group consisting of autoimmune lymphoproliferative disease, B-cell CLL, B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT type), nodal marginal zone lymphoma, splenic

marginal zone lymphoma, hairy cell leukemia, plasmacytoma, diffuse large

B-cell lymphoma, Burkitt lymphoma, multiple myeloma, indolent myeloma, smoldering myeloma, monoclonal gammopathy of unknown significance (MGUS), B-cell non-Hodgkin's lymphoma, small lymphocytic lymphoma, monoclonal immunoglobin deposition diseases, heavy chain diseases, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, precursor B-lymphoblastic leukemia/lymphoma, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, classical Hodgkin's lymphoma, nodular sclerosis Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, lymphocyte-rich classical Hodgkin's lymphoma, lymphocyte depleted Hodgkin's lymphoma, post-transplant lymphoproliferative disorder, and Waldenstrom's macroglobulinemia.

20. The method of claim 19, wherein said B-cell proliferative disorder is multiple myeloma.

21. The method of claim 1, 2, 7, 8, or 9, wherein said patient is not suffering from a comorbid immunoinflammatory disorder.

22. The method of claim 1, 2, 7, 8, or 9, wherein said antiproliferative

compound is selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D1 inhibitors, NF-kB inhibitors, anthracyclines, histone deacetylases, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, calcineurin antagonists, and IMiDs.

23. The method of claim 22, wherein said antiproliferative compound is selected from the compounds listed in Tables 3 and 4.

24. The method of claim 1, 2, 7, 8, or 9, wherein said antiproliferative compound is administered in a combination with at least a second antiproliferative compound.

25. The method of claim 24, wherein said combination is selected from the group consisting of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), VAD (vincristine, doxorubicin, and dexamethasone), MP (melphalan and prednisone), DT (dexamethasone and thalidomide), DM (dexamethasone and melphalan), DR (dexamethasone and Revlimid), DV (dexamethasone and Velcade), RV (Revlimid and Velcade), and cyclophosphamide and etoposide.

26. A kit comprising (i) an A2A receptor agonist and (ii) an antiproliferative compound in amounts that together are effective to treat a B-cell proliferative disorder.

27. A kit comprising (i) a PDE inhibitor and (ii) an antiproliferative compound other than a glucocorticoid in amounts that together are effective to treat a B-cell proliferative disorder.

28. A kit comprising (i) a PDE inhibitor having activity against at least two of PDE 2, 3, 4, and 7 and (ii) an antiproliferative compound in amounts that together are effective to treat a B-cell proliferative disorder.

29. A kit comprising (i) two or more PDE inhibitors that when combined

have activity against at least two of PDE 2, 3, 4, and 7 and (ii) an antiproliferative compound in amounts that together are effective to treat a B-cell proliferative disorder.

30. The kit of claims 26-29, wherein said antiproliferative compound is selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D1 inhibitors, NF-kB inhibitors, anthracyclines, histone deacetylases, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, calcineurin antagonists, and IMiDs.

31. The kit of claims 26-29, wherein said antiproliferative compound is selected from the compounds listed in Tables 3 and 4.

32. The kit of claims 26-29, further comprising at least a second antiproliferative compound in a combination with said antiproliferative compound.

33. The kit of claims 32, wherein said combination is selected from the group consisting of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), VAD (vincristine, doxorubicin, and dexamethasone), MP (melphalan and prednisone), DT (dexamethasone and thalidomide), DM (dexamethasone and melphalan), DR (dexamethasone and Revlimid), DV (dexamethasone and Velcade), RV (Revlimid and Velcade), and cyclophosphamide and etoposide.

34. The kit of claims 26-29, further comprising instructions for administering (i) and (ii) to a patient for the treatment of a B-cell proliferative disorder.

35. A pharmaceutical composition comprising (i) an A2A receptor agonist and (ii) an antiproliferative compound together in an amount effective to treat a B-cell proliferative disorder and (iii) a pharmaceutically acceptable carrier.

36. A pharmaceutical composition comprising (i) a PDE inhibitor and

(ii) an antiproliferative compound other than a glucocorticoid together in an amount effective to treat a B-cell proliferative disorder and (iii) a pharmaceutically acceptable carrier.

37. A pharmaceutical composition comprising (i) two or more PDE inhibitors that when combined have activity against at least two of PDE 2, 3, 4, and 7 and (ii) an antiproliferative compound together in an amount effective to treat a B-cell proliferative disorder and (iii) a pharmaceutically acceptable carrier.

38. A pharmaceutical composition comprising (i) a PDE inhibitor having activity against at least two of PDE 2, 3, 4, and 7 and (ii) an antiproliferative compound in amounts that together are effective to treat a B-cell proliferative disorder and (iii) a pharmaceutically acceptable carrier.

39. A kit comprising: (i) a composition comprising an A2A receptor agonist and an antiproliferative compound; and (ii) instructions for administering said composition to a patient for the treatment of a B-cell proliferative disorder.

40. A kit comprising: (i) an A2A receptor agonist; and (ii) instructions for administering said A2A receptor agonist with an antiproliferative compound to a patient for the treatment of a B-cell proliferative disorder.

41. A kit comprising: (i) a composition comprising a PDE inhibitor and an antiproliferative compound other than a glucocorticoid; and (ii) instructions for administering said composition to a patient for the treatment of a B-cell proliferative disorder.

42. A kit comprising: (i) a composition comprising a PDE inhibitor having activity against at least two of PDE 2, 3, 4, and 7 and an antiproliferative compound; and (ii) instructions for administering said composition to a patient for the treatment of a B-cell proliferative disorder.

43. A kit comprising: (i) a composition comprising two or more PDE inhibitors that when combined have activity against at least two of PDE 2, 3, 4, and 7 and an antiproliferative compound; and (iii) instructions for administering said composition to a patient for the treatment of a B-cell proliferative disorder.

44. A kit comprising: (i) a PDE inhibitor; and (ii) instructions for administering said PDE inhibitor and an antiproliferative compound to a patient for the treatment of a B-cell proliferative disorder, wherein said antiproliferative compound is not a glucocorticoid or said PDE inhibitor has activity against at least two of PDE 2, 3, 4, and 7.

45. A kit comprising: (i) two or more PDE inhibitors that when combined have activity against at least two of PDE2,3, 4, and 7; and (ii) instructions for administering said two or more PDE inhibitors and an antiproliferative compound to a patient for the treatment of a B-cell proliferative disorder.

L25 ANSWER 14 OF 24 USPATFULL on STN

PI US 20090047243 A1 20090219

CLM What is claimed is:

1. A method of treating a B-cell proliferative disorder, said method comprising administering to a patient a combination of an A2A receptor agonist and a PDE inhibitor in amounts that together are effective to treat said B-cell proliferative disorder.

2. The method of claim 1, wherein said A2A receptor agonist is selected

from the group consisting of the compounds listed in Tables 1 and 2.

3. The method of claim 1, wherein said PDE inhibitor is selected from the group consisting of the compounds listed in Tables 3 and 4.

4. The method of claim 1, wherein said PDE inhibitor is active against at least two of PDE 2, 3, 4, and 7.

5. The method of claim 1, wherein said combination comprises two or more PDE inhibitors that when combined are active against at least two of PDE 2, 3, 4, and 7.

6. The method of claim 1, wherein said B-cell proliferative disorder is selected from the group consisting of autoimmune lymphoproliferative disease, B-cell CLL, B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma, follicular lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT type), nodal marginal zone lymphoma, splenic marginal zone lymphoma, hairy cell leukemia, plasmacytoma, diffuse large B-cell lymphoma, Burkitt lymphoma, multiple myeloma, indolent myeloma, smoldering myeloma, monoclonal

gammopathy of unlcnown significance (MGUS), B-cell non-Hodgkin's lymphoma, small lymphocytic lymphoma, monoclonal immunoglobin deposition diseases, heavy chain diseases, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, precursor B-lymphoblastic leukemia/lymphoma, Hodgkin's lymphoma, nodular lymphocyte predominant Hodgkin's lymphoma, classical Hodgkin's lymphoma, nodular sclerosis Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, lymphocyte-rich classical Hodgkin's lymphoma, lymphocyte depleted Hodgkin's lymphoma, post-transplant lymphoproliferative disorder, and Waldenstrom's macroglobulineamia.

7. The method of claim 1, wherein said B-cell proliferative disorder is multiple myeloma.

8. The method of claim 1, wherein said A2A receptor agonist and PDE inhibitor are administered simultaneously.

9. The method of claim 1, wherein said A2A receptor agonist and PDE inhibitor are administered within 14 days of one another.

10. The method of claim 1, wherein said patient is not suffering from a

comorbid immunoinflammatory disorder.

11. The method of claim 1, further comprising administering an antiproliferative compound.

12. The method of claim 11, wherein said antiproliferative compound is selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D1 inhibitors, NF-kB inhibitors, anthracyclines, histone deacetylases, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, calcineurin antagonists, and IMiDs.

13. The method of claim 11, wherein said antiproliferative compound is

selected from the compounds listed in Tables 5 and 6.

14. The method of claim 1, further comprising administering a combination of at least two antiproliferative compounds.

15. The method of claim 14, wherein said combination is selected from the group consisting of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), VAD (vincristine, doxorubicin, and dexamethasone), MP (melphalan and prednisone), DT (dexamethasone and thalidomide), DM (dexamethasone and melphalan), DR (dexamethasone and Revlimid), DV (dexamethasone and Velcade), RV (Revlimid and Velcade), and cyclophosphamide and etoposide.

16. The method of claim 1, further comprising administering IL-6, a compound that increases IL-6 expression, or an IL-6 receptor agonist to said patient.

17. The method of claim 1, wherein said PDE inhibitor is active against PDE 4.

18. A kit comprising (i) a PDE inhibitor and (ii) an A2A receptor agonist in an amount effective to treat a B-cell proliferative disorder.

19. A kit comprising (i) an A2A receptor agonist and (ii) a PDE inhibitor having activity against at least two of PDE 2, 3, 4, and 7.

20. A kit comprising (i) an A2A receptor agonist and (ii) two or more PDE inhibitors that when combined have activity against at least two of PDE 2, 3, 4, and 7.

21. A kit comprising (i) an A2A receptor agonist, (ii) a PDE inhibitor, and (iii) an antiproliferative compound.

22. The kit of claim 18-20, further comprising an antiproliferative compound.

23. The kit of claim 21-22, wherein said antiproliferative compound is selected from the group consisting of alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF alpha agonists/antagonists, endothelin A receptor antagonist, retinoic acid

receptor agonists, immuno-modulators, hormonal and antihormonal agents, photodynamic agents, tyrosine kinase inhibitors, antisense compounds, corticosteroids, HSP90 inhibitors, proteosome inhibitors, CD40 inhibitors, anti-CSI antibodies, FGFR3 inhibitors, VEGF inhibitors, MEK inhibitors, cyclin D1 inhibitors, NF-kB inhibitors, anthracyclines, histone deacetylases, kinesin inhibitors, phosphatase inhibitors, COX2 inhibitors, mTOR inhibitors, calcineurin antagonists, and IMiDs.

24. The kit of claims 21-22, further comprising at least a second antiproliferative compound in a combination with said antiproliferative compound.

25. The kit of claim 24, wherein said combination is selected from the group consisting of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), VAD (vincristine, doxorubicin, and dexamethasone), MP (melphalan and prednisone), DT (dexamethasone and thalidomide), DM (dexamethasone and melphalan), DR (dexamethasone and Revlimid), DV (dexamethasone and Velcade), RV (Revlimid and Velcade), and cyclophosphamide and etoposide.

26. A pharmaceutical composition comprising (i) a PDE inhibitor and (ii)

an A2A receptor agonist in an amount effective to treat a B-cell

proliferative disorder and (iii) a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising (i) an A2A receptor agonist and (ii) a PDE inhibitor having activity against at least two of PDE 2, 3, 4, and 7 and (iii) a pharmaceutically acceptable carrier.

28. A pharmaceutical composition comprising (i) an A2A receptor agonist and (ii) two or more PDE inhibitors that when combined have activity against at least two of PDE 2, 3, 4, and 7 and (iii) a pharmaceutically acceptable carrier.

29. A kit comprising: (i) a composition comprising an A2A receptor agonist and a PDE inhibitor; and (ii) instructions for administering said composition to a patient for the treatment of a B-cell proliferative disorder.

30. A kit comprising: (i) an A2A receptor agonist; and (ii) instructions for administering said A2A receptor agonist with a PDE inhibitor to a patient for the treatment of a B-cell proliferative disorder.

31. A kit comprising: (i) a PDE inhibitor; and (ii) instructions for administering said PDE inhibitor with an A2A receptor agonist to a

patient for the treatment of a B-cell proliferative disorder.

32. A kit comprising: (i) a PDE inhibitor; (ii) an A2A receptor agonist;

and (iii) instructions for administering said PDE inhibitor and said A2A

receptor agonist to a patient for the treatment of a B-cell

proliferative disorder.

33. The kit of any of claims 29-32, wherein said PDE inhibitor has

activity against at least two of PDE 2, 3, 4, and 7.

34. A kit comprising: (i) two or more PDE inhibitors that when combined

have activity against at least two of PDE2, 3, 4, and 7; (ii) an A2A

receptor agonist; and (iii) instructions for administering said two or

more PDE inhibitors and said A2A receptor agonist to a patient for the

treatment of a B-cell proliferative disorder.

L25 ANSWER 15 OF 24 USPATFULL on STN

PI US 20080317708 A1 20081225

CLM What is claimed is:

1-21. (canceled)

22. A method of treating multiple myeloma, which comprises administering to a patient having multiple myeloma from about 0.1 mg to about 10 mg per day of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione of the formula: ##STR9## or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

23. The method of claim 22, wherein the compound is ##STR10##

24. The method of claim 22, wherein the compound is a pharmaceutically acceptable salt.

25. The method of claim 22, wherein the compound is a pharmaceutically acceptable solvate.

26. The method of claim 22, wherein the compound is a pharmaceutically acceptable stereoisomer.

27. The method of claim 26, wherein the stereoisomer is an enantiomerically pure R isomer.

28. The method of claim 26, wherein the stereoisomer is an enantiomerically pure S isomer.

29. The method of claim 22, which further comprises administering a therapeutically effective amount of a second active agent.

30. The method of claim 29, wherein the second active agent is hematopoietic growth factor, a cytokine, or an anti-cancer agent.

31. The method of claim 29, wherein the second active agent is granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), interleukin (IL) or interferon (IFN), or a combination thereof.

32. The method of claim 29, wherein the second active agent is oblimersen, melphalan, topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, dexamethasone, doxorubicin, vincristine, dacarbazine, Ara-C, vinorelbine, prednisone, cyclophosphamide, bortezomib or arsenic trioxide, or a combination thereof.

33. The method of claim 22, which further comprises administering radiation therapy, hormonal therapy, biological therapy or immunotherapy.

34. The method of claim 22, wherein the multiple myeloma is relapsed,

refractory or resistant to conventional therapy.

35. The method of claim 22, wherein the compound is administered orally.

36. The method of claim 35, wherein the compound is administered in the form of a capsule or tablet.

37. The method of claim 22, wherein the compound is administered in an amount of from about 0.5 mg to about 5 mg per day.

38. The method of claim 22, wherein the compound is administered in an amount of about 0.5 mg, 1.5 mg, 2 mg, 4 mg, and 5 mg per day.

39. The method of claim 22, wherein the compound is administered in an amount of from about 0.5 mg to about 2 mg per day.

40. The method of claim 22, wherein the compound is administered in an amount of about 1 mg per day.

41. The method of claim 22, wherein the compound is administered cyclically.

42. The method of claim 41, wherein one cycle comprises four to six weeks.

43. The method of claim 41, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

44. The method of claim 41, wherein the compound is administered for four to twenty-four weeks with one to six weeks of rest.

45. The method of claim 22, wherein the compound is administered in an amount of from about 0.5 mg to about 5 mg per day for 21 days followed by seven days rest in a 28 day cycle.

46. The method of claim 22, wherein the multiple myeloma is smoldering myeloma, indolent myeloma, chemotherapy responsive multiple myeloma, refractory myeloma, relapsed myeloma, or relapsed and refractory Dune-Salmon stage III multiple myeloma.

47. A method of treating multiple myeloma, which comprises administering orally to a patient having multiple myeloma from about 0.1 mg to about 10 mg per day of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione of the formula: ##STR11## or a pharmaceutically acceptable salt, solvate or